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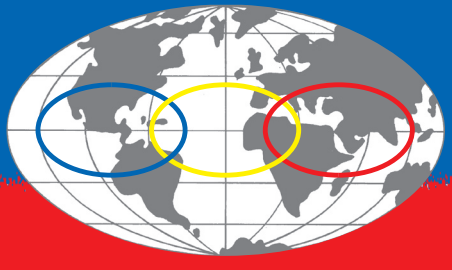

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GUIDELINES FOR VASCULAR ANOMALIES

EDIZIONI MINERVA MEDICA

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Società Italiana di Chirurgia Vascolare ed Endovascolare (SICVE)

Collegio Italiano di Flebologia (CIF)

Società Italiana di Angiologia e Patologia Vascolare (SIAPAV)

Società Italiana di Dermatologia medica, chirurgica, estetica e delle Malattie Sessualmente Trasmesse (SIDeMaST)

Società Italiana di Chirurgia Maxillo-Facciale (SICMF)

Società Italiana di Radiologia Medica e Interventistica (SIRM)

Società Italiana di Chirurgia Pediatrica (SICP)

Patient associations

Associazione Italiana Angiodisplasie ed Emangiomi Infantili (ILA)

Associazione Italiana Sindrome di Sturge Weber

Associazione HHT Onlus

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CONTENTS

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Introduction

The first Italian Guidelines GL on Vascular Malformations were created in 2014[1] by SISAV which, after 6 years, intends to update them according to the recently published studies and the most current scientific-technological innovations. To ensure that the recommendations on the subject are shared as much as possible and to facilitate their use on the territory, the main Scientific Societies in this field were also involved: SICVE, CIF, SIAPAV, SIDEMAST, SICMF, SIRM and SICP. Considering that the congenital pathologies here described belong to the group of Rare Diseases see Legislative Decree 12/01/2017 of the Ministry of Health on LEA, these Guidelines have been compiled with the aim of allowing medical colleagues GPs, pediatricians, radiologists, dermatologists, vascular surgeons, plastic surgeons, maxillofacial surgeons, etc. who find themselves managing any affected patients to outline the best diagnostic-therapeutic path. The distribution of these Guidelines to professional figures in the area will also have an important economic impact, as it will reduce the number of medical services performed on the patient before arriving at the diagnosis and definition of their pathology, with consequent benefit also for the psychological well-being.

The main objectives that we set ourselves in drafting this update are:

- to indicate the new classification criteria for a correct nosographical framing of the diseases in question;
- to identify specific diagnostic protocols to optimize the instrumental examination process;
- to define the current indications and the results of the different treatment methods to direct towards the most suitable therapeutic strategy.

Definition

Vascular Anomalies constitute a heterogeneous group of pathologies of the circulatory system characterized by morpho-structural and/or functional alterations of various nature, severity and extent that can affect any type of blood and/or lymphatic vessel, of any caliber and anatomical district.[1] They represent a problem of great medical and social importance as they are disabling diseases that occur in children or young people with serious functional, esthetic, and psychological disruptions.

Etiology

Vascular anomalies are caused by errors in the embryonic development of vessels, on a multifactorial genetic basis. In most cases, these are sporadic forms, which occur in subjects with a negative family history. However, hereditary forms are known, and they are related to genetic alterations of various angiogenic factors that regulate the development of vessels during embryogenesis.[2-4]

Epidemiology

The global incidence of vascular anomalies in the population currently remains a non-univocal data. Several studies with numerous samples report estimated values around 4.5% for vascular anomalies. Regarding vascular tumors, the incidence is about 5%, in particular with reference to the infantile hemangioma which is the most frequent anomaly.[5-7]

Classification

The nosographical classification of vascular anomalies is still a source of considerable difficulties and controversies due to the heterogeneity of the clinical-pathological entities and the confusion generated by the medical terminology of the past. The need to speak a shared scientific language has led in recent decades to search for an international classification that offers the clinician a simple and pragmatic tool for the recognition and management of various vascular anomalies. In 1996 the International Society for the Study of Vascular Anomalies ISSVA approved a simple and schematic classification that represented the basis for the development of the subsequent classifications adopted by the ISSVA itself in 2014 and 2018 Table I,[1, 8, 9] which represents an evolution of the previous classification of Mulliken *et al.* of 1982. The ISSVA classification has the advantage of being simple and schematic. It distinguishes Vascular Anomalies into two main groups that radically differ on the anatomo-pathological level: vascular tumors, which are divided into 3 groups in relation to the degree of neoplastic aggressiveness, and Vascular malformations, which consist of embryogenic alterations of various districts of the circulatory system and are divided into simple and combined and, in relation to the hemody-

Table I.—*ISSVA Classification 2014-2018.*

Vascular anomalies
Vascular tumors
Benign
Locally aggressive o borderline
Malignant
Simple vascular malformations
Capillary malformations CM
Lymphatic malformations LM
Venous malformations VM
Arteriovenous malformations AVM
Arteriovenous fistula AVF
Combined vascular malformations
Capillary-venous malformation CVM
Capillary-lymphatic malformation CLM
Lymphatic-venous malformation LVM
Capillary-arteriovenous malformation CAVM
Capillary-lymphatic-venous malformation CLVM
Capillary-lymphatic-arteriovenous malformation CLAVM
Capillary-venous-arteriovenous malformation CVAVM
Capillary-lymphatic-venous-arteriovenous malformation CLVAVM
Anomalies of major named vessels
Vascular malformations associated with other anomalies

namic characteristics, are divided into two main subtypes high and low flow to which are added the complex and/or combined forms.[1, 6, 7] Finally, both for Vascular Tumors and Vascular Malformations, a classification into subtypes has been elaborated and it will be presented separately in the respective chapters of these guidelines. This subdivision allows to outline the best diagnostic-therapeutic path for these pathologies.

Conclusions

As rare pathologies, vascular anomalies are far from usual general health management, and this makes the patient's path difficult both from a bureaucratic and a medical point of view. Therefore, drafting and dissemination of these Guidelines aims to maximize patient support through a greater awareness in the treating physicians. In this way it will be possible to reduce the number of health services provided before reaching the diagnosis and treatment, with a consequent reduction in the economic impact. Above all, the patient will benefit from a functional and psychological standpoint. The needs of these patients represent the focus of our work and for this reason several associations were involved in drafting these Guidelines: the ILA Italian Association of Angiodysplasias; the Italian Association of Sturge Weber Syndrome; the HHT Rendu Osler Weber Syndrome ONLUS. These associations played an important role in interviewing the patients regarding their disease and their satisfaction of the treatments received. Patients with rare vascular disorders vascular anomalies often must undertake long journeys to obtain a correct diagnosis. Almost every patient has doubts and/or Questions, sometimes even distressful, which have not been fully answered; on the other hand, the physician finds in the rarity of the disease an important obstacle to make a precise diagnosis. Therefore, the role of patient's Associations is crucial in helping to build an adequate diagnostic-therapeutic process. Since its establishment in 2012, the SISAV Italian Society for the Study of Vascular Anomalies has the primary objective of bringing together all the professional operators, both medical and non-medical, in a scientific community, who are dedicated to the research, diagnosis and treatment of vascular anomalies. By grouping different disciplines and specialties, the SISAV represents a unique entity in the panorama of Medical Scientific Societies, and it statutorily is an expression of the concept of multidisciplinarity through which Vascular Anomalies must be addressed today.

The General Coordinators of the Guidelines:
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Methodology

These Guidelines revise and update the Italian Guidelines on Vascular Malformations[1] published at the end of 2014 by SISAV. The methodology followed in this update is SIGN-GRADE version,[2] according to the methodological and practical indications provided by the Italian National Center for Clinical Excellence, Quality and Safety of Care CNEC.[3, 4] These guidelines were developed according to the AGREE quality of reporting checklist[5] and, once completed, were evaluated using the AGREE II tool.[6]

Composition of the working group

The working group was multidisciplinary and included specialists experienced in the following specialties: dermatology, vascular surgery and angiology, general surgery, plastic surgery, diagnostic and interventional radiology and neuroradiology, maxillo-facial surgery, pathological anatomy and histopathology, medical and molecular genetics, lymphology, phlebology, pediatric surgery, and hematology. In addition to SISAV, the main scientific societies related to the topics addressed were involved: SICVE, CIF, SIAPAV, SIDEMAST, SICMF, SIRM and SICP. The Italian Association of Angiodysplasias and Infantile Hemangiomas ILA, the Italian Association of Sturge Weber Syndrome and the HHT Onlus Association were also involved in the process.

Editorial independence

No external funding was received for the drafting of these guidelines. All the authors have completed the conflict-of-interest disclosure form adapted from the Methodological Manual to produce clinical practice guidelines of the "Sistema Nazionale Linee Guida" (SNLG). The disclosures are available on the SISAV website (http://sisav.eu/conflitti-dinteresse/). All authors have declared that they have no financial, professional, or other conflicts of interest related to the topics covered in these Guidelines.

Development of PICO questions

The first methodological step has been the formulation of clinical Questions structured according to the PICO model "population," "intervention," "comparison," and "outcome" according to which the recommendations were produced. The PICO Questions were jointly formulated by the multidisciplinary panel of authors.

Systematic review of the literature

The authors carried out systematic reviews of the literature for each PICO Question or for homogeneous groups of Questions. For the chapter about complex vascular malformations, literature searches were carried out for individual diseases. Searches were performed in PubMed, in the Cochrane Database of Systematic Reviews CDSR and the in Cochrane Central Register of Controlled Trials CENTRAL. The searches were limited to the period from January 2015 onwards, thus updating the previous SISAV guidelines that were completed in December 2014.

Selection process and critical appraisal of the literature

Literature selection was performed independently by pairs of authors for each clinical Question or for each topic, based on predefined inclusion criteria related to the PICO elements and to the considered study designs. The first selection was done by reading the title and abstract, while the second selection was done by examining the full texts of selected articles. Any discrepancy between the two authors was resolved by discussion. Two authors independently assessed the methodological quality of each included article through specific qualitative checklists provided by the SIGN-GRADE version methodology process. These checklists were used to assess the quality of systematic reviews/meta-analyses, randomized clinical trials RCTs, cohort studies, case-control studies, and diagnostic accuracy studies. The quality of the case series was assessed through the Institute of Health Economics IHE checklist,[7] while the quality of the case reports was assessed through the Case reports guidelines CARE checklist.[8] In the event that other international guidelines were used as an evidence basis, these were previously assessed using the AGREE II checklist, considering a total score of 60% as a minimum acceptability threshold Dimensions 3 and 6: minimum 50%, as indicated in the CNEC Operating Manual.[3] The levels of evidence attributable to the different study designs evaluated through the checklists are shown in Table I.

Table I.—*Levels of evidence.*

1++	High quality meta-analyses, systematic reviews of randomized clinical trials, randomized clinical trials with a very low bias risk factor.
1+	Well conducted meta-analyses, systematic reviews, randomized clinical trials with low bias risk factor.
1-	Meta-analyses, systematic reviews, randomized clinical trials with high bias risk factor.
2++	High quality systematic reviews related to the case-control studies or cohort studies; high quality case-control studies or cohort studies with very low confounding factor risk or bias and a very high probability of a random reaction.
2+	Well conducted case-control studies or cohort control studies with a low confounding factor or bias and a moderate probability of a random reaction.
2-	Case-control studies or cohort control studies with a very high confounding factor or bias and a significant risk of a random reaction.
3	Non- analytic studies, *e.g.*, case report and/or examples of clinical cases
4	Expert advice

From evidence to recommendations

The described methodology provides that, once the evaluation of the methodological quality of the included articles has been completed, the authors filled the Considered Judgment form for each clinical Question. This module included the following nine items: 1) reliability of the studies in the body of evidence; 2) consistency of their results; 3) relevance of the studies to the target population; 4) concerns about publication bias; 5) balancing benefits and harms; 6) Impact on patients; 7) Feasibility in the context where the GL will be used; 8) recommendations, specifying the strength and direction, and the overall level of evidence; and 9) recommendations for research.

Formulation of the recommendations

Once the compilation of all the Considered Judgments was completed, the authors presented and discussed them during a plenary meeting held in Rome on 12/09/2020. Following the presentation, an informal process to reach a consensus on the wording, strength and direction of the recommendations took place.

Recommendations are formulated on two levels: strong and weak. Normally, high quality evidence from well-conducted studies leads to a strong recommendation, but it may happen that, by evaluating the differences between the population described in the studies and the target population, patient acceptance and feasibility of the intervention, the recommendation is indicated as "weak." Conversely, there may be circumstances in which the evidence is technically modest, but there are no negative or controversial aspects of the treatment, and the clinical importance of the topic is such that it still leads to a strong recommendation. The good clinical practice GPP points are used to support the decisions of the guidelines' users, offering indications by the panel of authors based on their clinical experience, even in the case of scarce evidence, on issues deemed essential to good clinical practice. A summary of the degrees of recommendation is provided below Table II.

External review

The final version of the guidelines GL was sent for external review to independent experts on the covered topics and to representatives of patient groups, to receive their comments and change proposals. The reviewers were also asked to indicate any facilitating factors and obstacles to the application of the Guideline and suggestions and tools for implementation.

Procedure for updating the guideline

It is planned to update the GL every three years, starting from the date of publication on the SNLG website. The methodology followed in the update will be the same used in this version, or a similar methodology based on the

Table II.—*Degrees of recommendation.*

Medical judgement	Recommendation
Side effects clearly outweigh the desired effects	Recommendation strong against
Side effects likely outweigh the desired effects	Recommendation weak against
Balance between side effects and desired effects is in close balance or uncertain	Recommendation for research and limited use in trials
Desired effects probably outweigh the side effects	Recommendation weak in favor/pro
Desired effects clearly outweigh the side effects	Recommendation strong in favor/pro
Recommended best practice based on the clinical experience of the panel drafting the guideline	Recommendation strong in favor of/pro Point of good clinical practice GPP

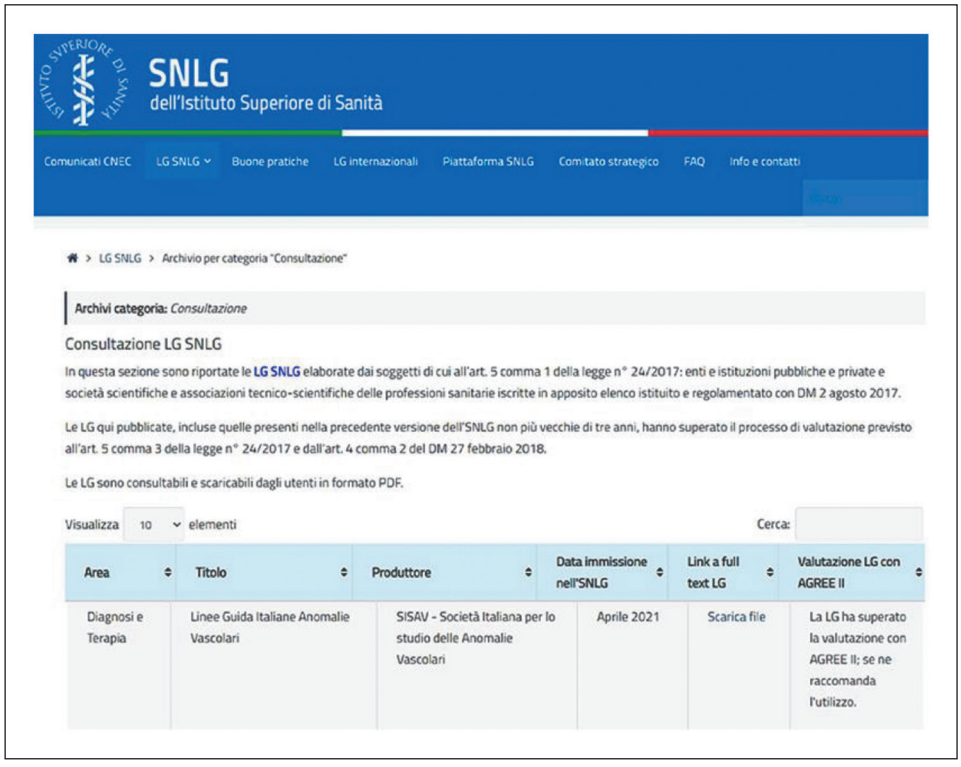

Figure 1.—Approval Guidelines SNLG.

GRADE approach. Literature search will start from the date of the present searches.

Considerations regarding the applicability of the recommendations

In a special point of the Considered Judgment, the authors panel expressed some considerations regarding the applicability of the measures recommended with respect to the context in which the guideline will be applied. In particular, the Authors considered: feasibility of interventions in the whole national context or only in special centers of level; experienced healthcare professionals; financial resources, medical staff, or other resources necessary for the implementation of the recommendations. Further considerations about the applicability of the recommendations and suggestions for improving implementation came from externa auditors.

The considerations of the applicability were considered by the authors panel in formulating recommendations (Figure 1).

Reporting

The guideline has been elaborated following the indications of the AGREE quality of reporting.

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Guidelines for vascular tumors

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Vascular tumors

Classification

The classification adopted by the "International Society for the Study of Vascular Anomalies" ISSVA, and subsequently updated and expanded in 2018,[1] divides vascular tumors into benign, locally aggressive, and malignant neoplasms. Our chapter will treat benign vascular tumors and kaposiform hemangioendothelioma which is one of the locally aggressive ones.

Benign vascular tumors are divided into:

- infantile hemangioma;
- congenital hemangiomas:
  - rapidly involutive RICH (these tumors can be associated with thrombocytopenia and, in the case of tufted angioma, with consumption coagulopathy Kasabach-Merritt phenomenon);
  - non-involutive NICH;
  - partially involutive PICH;
- tufted angioma (these tumors can be associated with thrombocytopenia and, in the case of tufted angioma, with consumption coagulopathy Kasabach-Merritt phenomenon);
- spindle cell hemangioma;
- epithelioid hemangioma;
- pyogenic granuloma also known as lobular capillary hemangioma;
- others – hemosiderotic targetoid hemangioma, microvenular hemangioma, anastomosing hemangioma, glomeruloid hemangioma, papillary hemangioma, papillary intravascular endothelial hyperplasia, cutaneous epithelioid angiomatous nodule, acquired elastotic hemangioma, littoral cell hemangioma of the spleen;
- related lesions – angiomatous eccrine hamartoma, reactive angioendotheliomatosis, bacillary angiomatosis.

Infantile hemangioma

Classification

Infantile hemangiomas IH are currently distinguished:

- based on the anatomical-clinical level in:
  - superficial IH – exophytic growth with respect to the cutaneous level;
  - deep EI – characterized by a development in the thickness of the integuments;
  - mixed EI;
- based on the topographical distribution in:
  - focal;
  - multifocal;
  - segmental;
  - eruptive.

Epidemiology and pathogenesis

IH is very frequent with a prevalence in the pediatric population of 3-10%.[2]

The etiopathogenesis is still unknown and it seems to be multifactorial. The risk factors are the following: female gender, Caucasian race, prematurity, Caesarean section, twin pregnancy, advanced maternal age, placenta previa and pre-eclampsia[2]. Many data suggest a clonal proliferation of endothelial cells that produce vasculogenesis. The causes mainly suspected in the literature are hypoxia,[3] placental embolization, multipotent stem cells, somatic mutation. The mediators involved in the pathogenesis of vascular proliferation are VEGF, GLUT1, IGF-2, the mTOR complex, angiopoietins ANG-1 and ANG-2, E-selectin, and the notch pathway.[4]

Natural history

IH is sometimes present at birth, but it most frequently appears in the first weeks of life. In some cases, it is preceded by a pallor, a pale bluish spot or an area covered with fine telangiectasias which represents the lesion precursor. The IH life cycle is divided into three phases: 1) rapid proliferative phase 0-1 year; 2) regression phase 1-5 years; and 3) involute phase 5-10 years:[5]

- IH reaches the 80% of its volume in the initial phase of proliferation, completing its growth almost always in the first 5-6 months. Only 3% of IH grows beyond the 9th month of life. The superficial forms generally grow up until the 5th month, while the deep ones and the segmental

ones manifest themselves later and continue to grow for a longer period even up to 18 months;

• the regression phase is characterized by a softening of the lesion and a discoloration starting from the central area, with a progressive reduction in volume and a decrease in the vascularity;

• the involute phase is characterized by the complete or almost complete regression, sometimes with scarring outcomes such as loose skin, atrophy, telangiectasias and/or fibroadipose tissue. Superficial IHs present a greater risk of scar residues than deep ones. It is important to closely monitor the IH when it shows a whitening during the first 3 months, as it can be an early sign of ulceration rather than regression.[6]

Clinical picture

Superficial IH

Superficial IH appears as a papular or nodular lesion, red or purplish red in color, with a smooth or lobulated surface, with a tense elastic consistency; its base is rarely pedunculated (dimensions are variable, as they can be from a few millimeters up to the involvement of an extended area entire limb, half-trunk, etc.).

Deep IH

Deep IH appears as an elastic nodular swelling, generally well defined, covered with skin of normal color, bluish or with telangiectasias.

Mixed IH

Mixed IH shows to have both components.

IHs can be localized in any part of the body, with a preference for the head and neck district, especially above bony prominences mid-facial area. Segmental lesions may be associated with underlying abnormalities, *e.g.*, S. PHACES in the case of extensive facial hemangioma or "pelvis "(EI perineum, external genital malformations, lipomyelomeningocele, visceral anomalies, imperforate anus or skin tag), "sacral" (spinal dysraphism, anogenital anomalies, skin anomalies, renal or urological abnormalities, lumbosacral angioma), and "lumbar" (IE of the lower body region, urogenital abnormalities, ulceration, myelopathy, skeletal abnormalities, anorectal malformations, arterial and renal abnormalities) in the presence of anogenital or lumbosacral midline IE.

The most serious malformation frequently associated with pelvis/sacral/lumbar is lipomyelomeningocele.

Spine and abdominal-pelvic MRI examinations are indicated in all neonates with segmental, midline lumbosacral or perineum IH, even if neurologically asymptomatic.

PHACES syndrome

PHACES syndrome was described by I. Frieden in 1996 as PHACE. The final S correspondent to the sternal defect was added later. Females are more affected than males 9/1 ratio. Segmental IHs seem to be consequent to tissue suffering probably from a vascular defect of the affected skin territory, in fact they often begin at birth with a large anemic area. PHACES is an acronym that stands for: P – malformation of the posterior fossa; H – hemangioma; A – arterial anomalies, especially aorta; C – heart defects; E – ocular anomalies; and S – sternal or supra-umbilical raphe defects. In most cases this syndrome occurs with incomplete expression, but a segmental hemangioma of the face is almost always present, sometimes with a beard distribution involving the following regions: mandibular region, preauricular region, chin, lower lip, neck and sometimes sternum, or the upper limb with extension to the lateral thorax region.[7]

Infantile hemangiomas with minimal or arrested growth IHMAG

It is a rare variety of IH. Clinically it is characterized by vascular patches formed by fine or coarse telangiectasias with a reticular aspect on which there may appear areas of proliferation 30% of cases. These areas most often are represented by angiomatous papules arranged mostly on the periphery of the lesions. By definition, the proliferative component does not exceed 30% of the total area. The IHMAG often appears surrounded by a vasoconstriction halo. The lower part of the body especially the limbs, the perineal region and the buttocks are the most affected sites. A possible complication is ulceration, more frequently in the perineal localization. Sometimes it is associated with hyper- or hypotrophy of the involved tissues. IHMAG differs from classical IH not only for the morphological aspect and the low proliferation rate, but also because of the onset period as it is mostly congenital and of the frequent absence of common IH-related risk factors. Segmental IHMAG can also be associated with dysraphism and structural anomalies, especially if located in the lower part of the body.

VISCERAL IHs

Visceral localizations are rare, but probably underestimated. The liver localization must be investigated by ultrasound in case of multiple eruptive hemangiomas miliary hemangiomatosis, in children younger than 6 months with more than 5 nodular hemangiomas, in those with hepatomegaly or with signs of congestive heart disease. Hepatic hemangiomas can be focal, multifocal, or diffuse.[8, 9]

Other extracutaneous localizations are possible at the laryngeal level in case of segmental parotid hemangiomas, and more rarely in the central nervous system intracranial or intraspinal. To ensure prompt specialist assessment and reduction of the potential risk of complications, the identification of high-risk infantile hemangiomas is indicated.

High-risk IHs are divided into:

- life-threatening lesions obstructive subglottic IHs, large IHs causing heart or liver failure;
- lesions at risk of functional impact peri-orbital, nasal, labial, laryngo-tracheal, joints, auditory canal;
- lesions at risk of aesthetic outcomes with psychological relevance localized on the glabella, nose, filter, chin, cheek, lips with deformity of the mouth, mammary gland in females or ulcerated and unresponsive to local dressings;
- lesions at risk for structural anomalies, *e.g.*, PHACES or lumbar.[10–12]

In the case of IH at risk of complications, the patient must be early addressed to a referral center to aim for a prompt intervention and better therapeutic results.

To decide whether to address the patient to a referral center, the pediatrician can help himself with the Infantile Hemangioma Referral Score IHReS,[13] a validated evaluation scale developed by a group of international experts and tested by European and Italian pediatricians. The IHReS goal is to improve the ability of healthcare professionals to decide when address patients with IH to a referral center. The first part is made of simple YES/NO Questions to identify of the following risk factors:

- complications or potential risk of complications ulceration, visual impairment, feeding difficulties, laryngeal stridor;
- localization in the middle third of the face and/or ears;
- localization in the mammary region in females;
- localization in the lumbosacral midline;
- amplitude ≥4 cm focal or segmental;
- number of hemangiomas ≥5.

In case of an affirmative answer, the patient should be sent to a referral center. If all the answers were negative, a more detailed table is compiled regarding the site of the hemangioma, the size of the largest hemangioma, the current age of the child and the growth of the hemangioma in the last two weeks. With a score ≥4, the patient must be sent to a referral center. If the score is <4, the patient will be monitored by his/her caregiver, who will repeat the scale assessment at each follow-up visit for the first 6 months.

Diagnosis

IH diagnosis is generally clinical. Some localizations require a multi-specialist approach. In particular, an ophthalmologist is needed in case of periorbital IHs, while an otolaryngologist is needed in case of laryngeal and auricular IHs. The cardiologist should be involved in the search for cardiac anomalies associated with segmental forms and in the case of heart failure risk due to hepatic hemangiomas. The neurosurgeon is indispensable for the evaluation of brain abnormalities associated with the PHACE syndrome.

Diagnostic investigations

The first investigation choice in case of diagnostic doubt is the eco-color-doppler. In rare cases, especially for deep lesions, histological confirmation might be required Table I.

However, in peculiar cases additional in-depth investigations are necessary: for example, brain or abdominal-pelvic MRI, echocardiography and ophthalmological evaluation are necessary to investigate syndromic forms. Eye counseling is also needed for all children with periorbital IH. In addition, the echocardiogram is indicated as a screening exam for those patients suffering from large segmental hemangiomas and in children with hepatic hemangiomas and significant arteriovenous shunts.

Question 1

What diagnostic investigations need to be carried out in patients with HI "beard" distribution and laryngeal stridor?

The following recommendation was imported from previous SISAV guidelines of 2015. Recent literature review revealed no evidence of changes in previous recommendations.

Recommendations

Airway endoscopy must be performed in patients with even small "beard" IH and stridor to investigate a laryngeal IH and to start an early treatment.

Strong recommendation in favor, Level of evidence 3

A screening of liver function and coagulation is indicated in all those patients with multifocal hepatic hemangiomas, while thyroid function exams are necessary in case of extensive or numerous multifocal IHs.[14]

Imaging of vascular tumors

Ultrasound, integrated with color-Doppler technique, is the first choice, as it is widely available, inexpensive, and it allows an evaluation of the architecture, vascularization,

TABLE I.—*Histopathology of vascular tumors.*

	Histological pattern	
Type of hemangioma	Benign tumors	Immunohistochemical
Infantile hemangioma	Growth pattern: well localized, lobulated. Different evolutionary aspects: Early stage/proliferative – capillary vessels from the lumen nearly virtual, swollen endothelial cells, mitotically active cells and prominent pericytes. Late stage/involuting – progressive expansion of the vascular lumen, flattening and apoptosis of endothelial cells, thickening of the vascular basal membrane and interposition of fibroadipose tissue	Positive endothelium for: common endothelial markers CD31, CD34, Fli-1 and ERG WT-1, GLUT-1
Congenital hemangioma	Growth pattern: well localized Three subtypes: Quickly involuting RICH – small capillaries with prominent endothelium in the lumen and thin basement membrane and regressive aspects consisting in thickening of basement capillary membrane, fibrosis, outbreaks of chronic phlogosis, dystrophic calcification, thrombosis, and hemosiderin deposits Non involuting NICH – large lobules at net margins consisting of capillaries with endothelial at times prominent in the lumen and thin basement membrane thickened at times. Wide inter-lobular fibrous space with draining vessels, at times to thickened muscle wall simulated malformations and arteria -venous fistula Partially involuting PICH – undistinguishable histological appearances from NICH Growth pattern: well localized, lobulated	Positive endothelium for: common endothelial markers CD31, CD34, Fli-1 and ERG; GLUT-1 negative
Epithelioid hemangioma	Small vessels with epithelimorphum endothelium at times obliterating the vascular lumen, no atypypes and with minimal miotic activity. Presence of perivascular pericytes, single wire. In some cases, it associates intense chronic inflammatory infiltrate and in acute to eosinophilic granulocyte component	Positive endothelium for: common endothelial markers CD31, CD34, ed ERG rare cytokeratin and FOSB
"Tufted" hemangioma	Growth pattern: with multiple lobules at dermal site and hypodermic with a cannonball ("palle di cannone") appearance, often delimited by dermis crossed by lymphatic vessels. The capillaries constituting the lobules have rounded lumen or at long slot, with endothelium from bulge to fusate with limited mitoses and no atypies, with discrete pericitary component. Intermediate tumors locally aggressive	Positive endothelium for: common endothelial markers CD31, CD34, ed ERG; lymphatic markersD2-40; LYVE1 e PROX1
Kaposiform hemangioendothelioma	Growth pattern: lobular/infiltrative to dermo-hypodermic site, in superficial and deep soft tissues with fibrous bands between which alternate aspects similar to hemangiomas and sarcoma of Kaposi. Endothelial cells without atypia, with cytoplasmic vacuolation and minimal activity. Possible micro-thrombus in luminal site. Intermediate tumors rare metastasizing	Positive endothelium for: common endothelial markers CD31, CD34, ed ERG; lymphatic markers D2-40; LYVE1 e PROX1
Pseudomiogenic hemangioendothelioma	Growth pattern: infiltrative, mainly in loose fascicles and single elements in deep soft tissues. Fused/rhabdomyoblastic endothelial elements, with nucleulated nucleus, moderate atypy and minimal mitotic activity. Cancerous tumors	Positive endothelium for: cytokeratin AE1/AE3; endothelial markers Fly-1 ed ERG; FOBS
Epitheliod emangioendotelioma	Growth pattern: angiocentrifugal with expansive/infiltrative growth in sclerotic stroma/myxohyaline. Epitheliomorph/stellariform elements in cords and single elements in mixo-hyaline stroma, with pale pink cytoplasm "frosted glass," possible presence of some intracytoplasmic erythrocytes, roundish/reniform nucleus, mitosis, and rare necrosis.	Positive endothelium for: endothelial markers in variable % CD31, CD34, D2-40; Fli-1 ed ERG; cytokeratin; CAMTA1
Angiosarcoma	Growth pattern: infiltrative, with the formation of irregular lumens, cords, and single elements. Endothelial elements at various degrees of atypy, with mitotic activity and variable necrosis	Positive endothelium for: endothelial markers in variable % CD31, CD34, D2-40; Fli-1 ed ERG; cytokeratin in % variable; MYC

and flow dynamics of a vascular tumor. Its limits are the operator-dependency results and the difficulty in studying deeper and more extensive lesions. Magnetic resonance imaging MRI is the second method of choice. Thanks to multiplanar imaging and higher contrast resolution for soft tissues, it is optimal to assess the disease extension and its relationships with surrounding anatomical structures *e.g.,* in syndromic forms. Moreover, it allows to study those lesions located in deep soft tissues and that are clinically difficult to diagnose. The MRI can also help to define the nature of a suspected lesion, while angiographic sequences allow to study the anatomy and the vascular dynamics. The MRI limits are the long examination execution time and the need for general anesthesia/sedation. Computed tomography CT is avoided for the study of vascular tumors in children to reduce the exposure to ionizing radiation and given the poor contrast resolution with soft tissues. It may be necessary in cases of bone lesions, particularly in the head and neck region.[15–18]

Question 2
In children with clinical suspicion of congenital or infantile hemangioma, which tests are accurate for radiological diagnosis?

Imaging is rarely used for benign vascular tumors, except for uncertain clinical diagnoses deep lesions which are objectively not evaluable and for the evaluation of a deep lesion extent or to search for associated anomalies or to monitor the response to medical therapy.[19–21] When necessary, color Doppler ultrasound is the first-choice exam for the diagnosis.[15–18, 22, 23] In particular, Echocolor-Doppler features shared by the two types of hemangiomas are: cutaneous-subcutaneous localization, basically well-defined margins, variable structure, high vascular density, arterial and venous flow at Doppler with high systolic peak, low resistance index RI. Ultrasound features that significantly differentiate congenital hemangiomas from infants are visibility of the vascular structures - appreciable in B-mode beyond the deep fascia up to the muscle - presence of calcifications, possible poorly defined margins and possible arteriovenous microshunts in particular in NICH. Furthermore, the diameter of the vascular structures visible in B-mode in congenital hemangiomas is greater in RICH and PICH, while the vascular density is greater in NICH.[17, 20, 24] In a 2020 retrospective study Gong defines the ultrasound and color-Doppler characteristics of infantile and congenital hemangiomas.[24] Furthermore, based on elastosonography, congenital hemangiomas were found to be "softer"/more elastic than IHs.[24, 25]

INTERPRETATION OF THE DATA

To answer Question 2, four non-systematic narrative reviews and five retrospective case series were analyzed.[16–21, 24–26] When necessary, ultrasound is the first exam choice. MRI is indicated for the assessment of the extent of the disease and for the differential diagnosis, especially for deep lesions that cannot be clinically evaluated. Elastosonography can support ultrasound in the evaluation of hemangiomas. There is consistency between the study analyzed and the expert judgment. Studies are relevant to the target population, include infantile and congenital hemangiomas and related ultrasound semeiotics. The benefit of this recommendation is to obtain the diagnosis of infantile and congenital hemangioma in clinically suspicious and/or uncertain cases by the means of differential diagnosis between non-invasive methods primarily ultrasound. A late diagnosis might be possible due to the inexperience of the operator since the ultrasound method is operator dependent. Considering the non-invasiveness, the ease of use and the wide availability between the facilities, the impact on patients is minimal compared to the important diagnostic advantage. The quality of the evidence, assessed through the checklist for systematic reviews, was found to be acceptable. The analysis of the studies shows a clear relevance for the target population, the conclusions are consistent and there is no potential bias.

Recommendations
Color Doppler ultrasound is the first-choice diagnostic tool for hemangiomas with an uncertain clinical diagnosis. *Strong recommendation in favor, level of evidence 3*

Question 3
In children with multiple cutaneous infantile hemangiomas, is the Doppler ultrasound an accurate test for the diagnosis of hepatic hemangiomatosis?

Iacobas recommends color Doppler ultrasound of the liver as an initial examination.[27] If the diagnosis remains uncertain, contrast-enhanced MRI should be done. Hepatic hemangiomas can be focal mostly congenital, multifocal, or diffuse mostly infantile. On ultrasound they appear as uniformly hypo- or hyperechoic formations for lesions less than 3 cm, the small ones generally homogeneous infantile while the larger ones >3 cm appear with a more complex and heterogeneous echo-structure due to calcifications, cystic components, and areas of fibrosis congenital. Color Doppler variability: signs of overflow with possible arteriovenous shunts or low systolic-diastolic speeds.

On MRI, hepatic hemangiomas are typically hypointense in T1W and hyperintense in T2W. Possible hyperintensity in T1W is due to blood, while hypointensity in T1W and T2W is due to fibrosis. The dynamic study after administration of contrast medium shows globular enhancement in the early stages followed by gradual centripetal filling in the late stages. In late sequences with hepatospecific contrast agent, hepatic hemangiomas appear hypointense compared to hepatic parenchyma. However, the integration of imaging with clinical-anamnestic and laboratory data a-feto-protein, AFP is necessary.[27] Serum AFP levels are generally normal in patients with infantile hepatic hemangiomas but may increase during the proliferative phase. However, they never reach such high levels as in patients with hepatoblastoma.[27, 28]

Xu reports the efficacy of the association between clinic and ultrasound in the diagnosis of infantile hepatic hemangiomas.[28] El-Ali described the findings of ultrasound with contrast medium for infantile and congenital hepatic hemangiomas.[29] The differential diagnosis is with hepatoblastoma or with neuroblastoma metastases. If hepatic focal lesions come detected after infancy, imaging is doubtful or the clinical history does not support the diagnosis of hemangioma, performing an MRI with contrast medium is recommended.[27, 30]

INTERPRETATION OF THE DATA

To answer Question 3, the following were identified: the American guidelines, a non-systematic narrative review, a retrospective case-control observational study and a retrospective review.[27–30]

Iacobas defines guidelines for the diagnosis and management of hemangiomas through a multidisciplinary consensus of experts based on the literature.[27] Xu reports that the association of the clinic with ultrasound is sufficient for the diagnosis of hepatic hemangiomas without having to resort to second-level imaging methods. [28] El-Alì *et al.* reports the utility of ultrasound with contrast medium for the diagnosis of hepatic hemangiomas.[29] There is consistency between the study analyzed and the expert judgment. The studies are relevant to the population target and include infantile and congenital hepatic hemangiomas and related radiological semeiotics. The benefit of the recommendation is to obtain the ultrasound diagnosis of hepatic hemangiomatosis in children with multiple cutaneous infantile hemangiomas without recourse to second level methods such as CT or MRI, more expensive, requiring exposure to ionizing radiation CT, anesthesia for the increased exam acquisition time RM. A late diagnosis might be possible due to the inexperience of the operator since the ultrasound method is operator dependent. Considering the non-invasive, ease of use and wide availability, the impact on patients is minimal compared to the important diagnostic advantage.

Recommendations

In children with multiple cutaneous infantile hemangiomas, the Doppler ultrasound is the most suitable test for the diagnosis of hepatic hemangiomatosis.

Strong recommendation in favor, level of evidence 2-

Question 4

In children with diffuse hepatic hemangiomatosis or with large cutaneous hemangioma which diagnostic tests are accurate to identify the presence of complications?

Possible complications of congenital hepatic hemangiomas are intralesional bleeding, thrombocytopenia, hypofibrinogenemia and heart failure. Diffuse infantile hepatic hemangiomatosis is at high risk of heart failure after birth in the proliferative phase, given the increase in size of the shunts and with a 16% mortality rate. This condition requires more monitoring and longer follow-up than other cutaneous multifocal forms. Although there is agreement on the need for serial ultrasound of the liver, a monitoring protocol has not yet been defined. However, the Liver Hemangioma Registry recommends ultrasound of the liver to be performed at progressively longer intervals, the first at two weeks and then every two weeks in case of stability. Adding two weeks to the interval after each stable evaluation. Monitoring of congenital hemangiomas is recommended for at least one year, until liver ultrasound shows stability of size and vascularity twice in a row. Continuous monitoring of infantile hemangiomas until complete involution is recommended.[27, 31, 32] Waelti determined whether there are ultrasound criteria associated with an increased risk of bleeding, ulceration, or heart failure for rapidly involutional congenital hemangiomas RICH. In particular, she distinguished three vessel categories within the RICH: "visible," "venous ectasias" and "venous lakes" and concluded that the latter two patterns are associated with an increased risk of bleeding and heart failure.[33]

INTERPRETATION OF THE DATA

To answer Question 4, there have been identified in literature one retrospective observational study and two case reports that reported the importance of ultrasound imaging for the identification of any complications in children with congenital cutaneous and hepatic hemangiomas. [27, 31–33] In

particular, Waelti identifies the "venous like" ultrasound pattern associated with the risk of heart failure and the "venous like" and "venous ectasia" patterns associated with the risk of bleeding.[33] There is consistency between the conclusions of the studies analyzed. High degree of coherence between studies. Studies are relevant to the target population and include cutaneous and visceral congenital hemangiomas. Establish careful monitoring and/or treatment of lesions at imaging risk of complications. Complications: bleeding, ulceration, or heart failure. Considering the non-invasiveness, ease of use and wide availability between the facilities, the impact on patients is minimal compared to an important diagnostic advantage.

Recommendations
Liver echo-color Doppler is indicated as the imaging method of choice for the identification of complications in children with diffuse hepatic hemangiomatosis or with large cutaneous hemangioma.
Strong recommendation in favor, level of evidence 3

Question 5
In children with segmental infantile cutaneous hemangioma, which diagnostic test is accurate to highlight deep localizations and/or any associated malformation?

Magnetic resonance imaging MRI is the reference method. Thanks to multiplanar imaging and higher contrast resolution for soft tissues, it is optimal for assessing the extent of disease and relationships with surrounding anatomical structures, *e.g.,* in syndromic forms or for clinically not diagnosable lesions located in deep soft tissues. It can possibly define the cellularity of a suspicious lesion, while the angiographic sequences allow the study of anatomy and vascular dynamics. The limits of MRI are the longer execution times of the examination and the need for general anesthesia/sedation.[15–18] Deep hemangiomas are iso-hypointense in T1W and hyperintense in T2W, have clear margins, might show internal flow-voids referable to vascular structures intralesional and intense enhancement after contrast medium.[20, 34] In case of suspicion of PHACE S syndrome, MRI/MRA of the brain and echocardiogram should always be performed and in case of suspected abnormalities, completion with cardio MRI and MRA of the aortic arch and epiaortics vessels is necessary. There is no consensus regarding the frequency of imaging checks. In some centers, in cases at high risk of cardio-vascular ischemic events, exams are performed every 3 months, while in others they are performed annually. Each case must be assessed individually.[35] In the syndromic forms like pelvis, lumbar, sacral, Subiabre-Ferrer Syndrome in accordance with the literature it is recommended to execute an ultrasound within 4-6 months, before the ossification of the posterior spinal elements ends. MRI should be performed, but not earlier than 6 months, when the adipose tissue around the filum terminus is well formed.[36]

INTERPRETATION OF THE DATA

To answer Question 5, there have been identified in the literature two retrospective observational studies, one non-systematic narrative review and a case report with review of the literature with reference to hemangiomas of the orbital and parotid regions and to syndromic forms PHACEs and lumbar/sacral.[20, 34–36] Although ultrasound is the first instance examination, MRI is the most informative to assess deep involvement. There is consistency between the conclusions of the studies analyzed. Studies are relevant to the target population. Correct management of deeply localized cutaneous hemangiomas and syndromic forms. Even if the main disadvantages of MRI are the cost and the need for anesthesia, the impact on patients is minimal compared to the important diagnostic advantage. Feasible even if not always widely available throughout the national context.

Recommendations
MRI is indicated as the imaging method of choice to highlight deep localizations and/or any associated abnormalities in children with infantile cutaneous hemangioma.
Strong recommendation in favor, level of evidence 3

Question 6
In patients with an uncertain clinical diagnosis of vascular tumor, what radiological investigations are necessary for the differential diagnosis with other vascular abnormalities and/or soft tissue lesions?

Vascular tumors are included in the group of soft tissue swellings which are divided into two categories: neoplastic and non-neoplastic lesions.[18] Tomà defines ultrasound as a first-choice exam – followed by MRI – thanks to its wide availability, lack of ionizing radiation and independence from anesthesia/sedation. [18] In particular, he reports the differential diagnosis modified by Kransdorf of soft tissue lesions based on the ultrasound pattern: for vascular tumors the differential diagnosis is based on the hypoechoic, hypervascular and hyperechoic lobulated pattern. Ding highlights the role of ultrasound in the differential diagnosis between deep infantile hemangioma and venous malformation, also emphasizing the usefulness of regarding elastosonography infantile hemangiomas appear less "elastic"

than malformations.[37] Zaltsberg defines the ultrasound findings of non-specific infantile hemangiomas and illustrates the differential diagnosis with soft tissue lesions with high vascular density.[38] However, ultrasound can be misleading because most pediatric soft tissue tumors can mimic a vascular anomaly and vice versa. Being able to distinguish the most common "imitators" of vascular anomalies is essential not only for an early and correct diagnosis but also for optimizing patient management.[18] Magnetic resonance imaging MRI is however the reference method in clinically and ultrasonographically suspicious cases.[15–18, 39, 40] However, in some districts such as the orbital one, MRI findings of IH and malignant tumors rhabdomyosarcoma overlap, making radiological differential diagnosis difficult. In these cases, Saito and Kralik report that diffusion sequences can help define the cellularity of the lesion under study: malignant tumors are frequently associated with increased cellularity, reduced extracellular space and large nuclei, and they exhibit diffusivity restriction with hyperintensity of signal in DWI sequences and low values of ADC, while hemangiomas show hypointensity in DWI sequences and high ADC values.[39, 40]

INTERPRETATION OF THE DATA

To answer Question 6, the following were identified: a non-systematic narrative review, a pictorial essay and three retrospective observational studies.[18, 37–40] Echo-color Doppler is the first-choice method, in particular for superficial lesions, due to its wide availability, low costs, absence of ionizing radiation and sedation. In particular, Tomà reports the differential diagnosis of soft tissue injuries based on ultrasound patterns. Due to the potential risks related to sedation/general anesthesia and those emerging for the accumulation of contrast media, MRI is the second-choice method and should be performed in case of non-diagnostic ultrasound examination. In particular, Kralik and Saito emphasize the usefulness of MRI diffusion sequences for the differential diagnosis between childhood hemangiomas and malignant soft tissue tumors in pediatric patients. There is consistency between the study analyzed and the expert judgment. Studies are relevant to the target population. The benefit of the recommendation is to offer differential radiological diagnosis for clinically suspicious and/or uncertain cases.

Recommendations

Color Doppler and MRI are indicated as imaging methods necessary for the differential diagnosis of vascular tumors with other vascular anomalies and/or soft tissue lesions.
Strong recommendation in favor, level of evidence 3

Histological diagnostics of vascular tumors

Histological diagnostics of vascular tumors require, as for all pathologies:

- clinical-pathological correlation;
- the use of immunohistochemical markers to support histological diagnostic hypotheses;
- knowledge of differential diagnostics.

Vascular tumors are characterized by a great variety of histotypes ranging from more frequent benign forms, particularly in the skin infantile hemangiomas, to rarer benign forms congenital hemangiomas, to intermediate-grade forms of malignancy, extremely rare hemangioendotheliomas, to malignant forms, rare and sometimes linked to recognize etiological factors such as postradiotherapy angiosarcoma and Kaposi's sarcoma in subjects suffering from AIDS.[41] In addition to the already numerous and recognized variety of histotypes, new entities have been described such as pseudomyogenic hemangioendothelioma [42] and plaque-like poikilodermal hemangioma. The latter is characterized by a "banded" vascular proliferation in the superficial dermis.[43] The aid of immunocytochemical investigations and the progressive discovery of antibodies have allowed and still allow to define them more and more precisely, in particular antibodies such as FOSB, MYC and CAMTA1 are the latter recognized as useful for the histological diagnosis respectively of pseudomyogenic hemangioendothelioma,[44–46] angiosarcoma, in particular postradiotherapy[47, 48] and epithelioid hemangioendothelioma.[49] The GLUT-1 immunostain is also confirmed to be of great help in the diagnosis of infantile hemangioma, regardless of the site.[50] While the clinical and imaging examination allow to diagnose most vascular tumors, the histological examination assumes importance in the differential diagnosis, especially with metastatic malignant epithelial neoplasms in some critical sites such as breast, kidney, and lung (Table I).[51–53]

Question 7

In patients with clinical suspicion of vascular tumor, are histological or imaging tests indicated to differentiate it from vascularized malignant lesions?

Magnetic resonance or other imaging tests do not seem to be able to replace the histological examination in the diagnosis of vascular tumors compared to richly vascularized neoplasms of another nature.[51, 52] MRI seems to play a significant role in atypical vertebral hemangiomas only.[53]

INTERPRETATION OF THE DATA

To answer Question 7, three studies[51–53] were identified. The recommendation derives from retrospective studies

on limited series, while prospective studies on more numerous series with direct comparison between the different diagnostic investigations would be necessary. The conclusions of the analyzed studies are limited to breast-based vascular lesions in a retrospective series of 27 patients which highlights the need to resort on histological examination as the clinical data and images are not diriment between benign and malignant lesions. In 2 clinical studies with internal organ neoplasms, one of which is retrospective on 15 patients with kidney injury, preoperative imaging does not seem to be able to differentiate hemangiomas and malignant tumors.[51-53] Experts agree that MRI or other imaging tests cannot replace histological examination in the diagnosis of vascular tumors compared to neoplasm that show a rich vascular nature. The only risk reported with the histological examination is bleeding; another limitation is the feasibility only in centers where it is possible to technically carry out the sample, which depends on the organ concerned; in addition, adequate histopathological experience is essential. Only in atypical vertebral hemangiomas magnetic resonance imaging seems to play a significant role. Studies are relevant to the target population and have no possible bias.

Recommendations
The histological examination is a useful aid to the clinic and to imaging investigations to differentiate benign vascular lesions from malignant lesions.
Weak recommendation in favor, level of evidence 3

Question 8
In patients undergoing histological examination for suspected vascular tumor, which histochemical/immunocytochemical stains are necessary for diagnostic purposes?

INTERPRETATION OF THE DATA

To answer Question 8, eight studies[43–50] were analyzed. Immunocytochemical determination for FOSB is specific and sensitive for the histological diagnosis of epithelioid hemangioma and pseudomyogenic hemangioendothelioma and is therefore useful for differential diagnosis with histologically similar entities cutaneous epithelioid angiomatous nodule, epithelioid hemangioendothelioma, angiosarcoma, epithelioid angiosarcoma and epithelioid sarcoma.[44] Immunocytochemical determination for Myc is very specific and not very sensitive for the histological diagnosis of secondary breast angiosarcomas and is associated with a poor prognosis.[47] High grade de novo angiosarcomas have a higher immunocytochemical expression of Myc than low grade ones.[48] Immunocytochemical determination for CAMTA1 is highly specific and sensitive for the histological diagnosis of epithelioid hemangioendothelioma.[49] A new variant characterized histologically by a "banded" vascular proliferation in the superficial dermis has been added to the list of hemangiomas.[43] Immunocytochemical determination for GLUT-1 is important for the diagnosis of oral cavity infantile hemangiomas.[50] Studies concur on the fact that MRI or other imaging tests do not seem to be able to replace the histological examination in the diagnosis of vascular tumors compared to other richly vascularized neoplasms.

Recommendations
Immunocytochemical investigations are recommended to define the diagnosis of vascular tumors. The GLUT-1 marker is of great help in the diagnosis of infantile hemangioma, regardless of the site. FASD antibodies, MYC and CAMTA1 are useful for the histological diagnosis of pseudomyogenic hemangioendothelioma, angiosarcoma postradiotherapy and epithelioid hemangioendothelioma, respectively.
Weak recommendation in favor, level of evidence 2-

Treatment

Treatment of IH is only needed in about 10-15% of cases. Therapeutic options are numerous: medical therapy, surgical therapy, laser treatment, sclerotherapy, or multimodal treatment. These different modalities can overlap with each other to stop the proliferative phase, accelerate the spontaneous involution of the lesions, prevent and correct early postinvolutionary outcomes.

Question 9
What are the indications to systemic treatment with propranolol in patients with IH?

The following recommendation was imported from previous SISAV guidelines of 2015. Recent literature review has revealed no evidence of changes in previous recommendations.

Recommendations
The indication for treatment is limited to life-threatening IHs high-output heart failure or obstruction/compression of the respiratory tract, IHs at risk of functional damage sight, nutrition, hearing and mNUk dexterity, IHs that determine significant aesthetic damage and/or permanent and ulcerated IHs that do not respond to standard topical treatments.
Strong recommendation in favor, level of evidence 4

Question 10
In children with infantile hemangioma at risk of complications in first-line treatment, is oral propranolol more efficacious and safer than oral corticosteroids?

Propranolol

Propranolol is the drug of choice for the treatment of IH, as a meta-analysis shows that oral propranolol is superior to any other treatment for IH and that can be used as first-line therapy at a dosage of 2 mg/kg/day.[54] Propranolol is a non-selective beta-adrenergic antagonist. The drug acts through a vasoconstrictive action, an inhibiting VEGF action and a long-term effect due to the induction of cellular apoptosis.[55] Contraindications to propranolol are asthma, hypotension, peripheral vascular disease, some heart conditions A/V block II and III, SSS, cardiogenic shock, bradycardia, heart failure, and Prinzmetal angina and pheochromocytoma.

INTERPRETATION OF THE DATA

To answer Question 10, a meta-analysis and a randomized clinical trial describing patients with EI [12, 54, 56] were identified in the literature. Yang's meta-analysis shows that oral propranolol is superior to any other treatment for IH and can be used as first-line therapy at a dosage of 2 mg/kg/day. Non-randomized trials and cohort studies are also included due to the limited sample size. The quality of the evidence was assessed using the checklist for systematic reviews and meta-analyzes, with the following results: high quality ++.[54]

Kim's randomized controlled study shows that propranolol is not inferior to the steroid in its therapeutic effect on IH. The study is not double-blind. The quality of the evidence was assessed using the checklist for randomized trials, with the following results: acceptable quality +.[56] The American guidelines were also analyzed by means of the AGREE Reporting 2016 Checklist, which identify oral propranolol as first-line therapy for IHs requiring treatment, with a strong recommendation.[12] Studies are consistent in indicating oral propranolol as first-line therapy in IHs requiring treatment. A randomized trial, meta-analysis and guideline are included. Treatment of IH with propranolol has been shown to have greater efficacy than steroids and a lower incidence of complications. Side effects are known but controllable and transient. Mostly they are sleep disturbances, bronchospasm, bradycardia, gastrointestinal disturbances, and hypoglycemia. In particular cases the drug dose may be lower than the recommended one, thus obtaining a minor result. For example, prematurity, low weight and PHACE syndrome.

Recommendations
In children with infantile hemangioma at risk of complications, oral propranolol is the first-line treatment since demonstrated greater efficacy and safety than oral corticosteroids.
Strong recommendation in favor, level of evidence 1++

Question 11
In order to reduce the risk of complications in the newborn/infant with infantile hemangioma, is the education of parents in the knowledge of the natural history of IH and therapeutic education for the home management of propranolol treatment indicated?

INTERPRETATION OF THE DATA

To answer Question 11, the American guidelines were analyzed, which state that therapeutic education of parents increases adherence to therapy and improves home management.[12] Education should include explanations on the pathology and its natural history, potential complications, and its evolution. If therapy is required, the specialist should educate parents about the drug, the dosage, possible adverse events, and the expected duration of treatment, also with the help of an information sheet. The evidence was assessed using the 2016 AGREE Reporting Checklist for guidelines with the following results: agreement of the evidence on the need to educate parents of patients with IH. The evidence analyzed also agrees with the expert opinion. The benefits outweigh the harms in implementing education strategies. The intervention is acceptable for parents and patients and indeed it improves home management by reducing outpatient or hospital access.

Recommendations
To reduce the risk of complications in the newborn/infant with infantile hemangioma, parental training in the knowledge of the natural history of IH and therapeutic education for the home management of propranolol therapy is indicated.
Strong recommendation in favor, level of evidence 4

Timing, dose, and treatment follow-up

Question 12
What are the preliminary investigations necessary for systematic TREATMENT with Propranolol in HI?

The following recommendations are imported from previous SISAV guidelines 2015.

Recommendation
A cardiology and ECG evaluation should be performed for treatment clearance.
Weak recommendation in favor with level of evidence 4

Question 13
What is the recommended timing for starting systemic therapy with Propranolol in HI?

The following recommendation was imported from previous SISAV guidelines of 2015. Recent literature review has revealed no evidence of changes in previous recommendations.

Recommendation
If indicated, treatment should be initiated as soon as possible.
Strong recommendation in favor, level of evidence 2+

Question 14
In which setting and with what precautions it is recommended to proceed to the administration of the first dose of the systemic therapy with propranol?

The following recommendation was imported from previous SISAV guidelines of 2015. Recent literature review has revealed no evidence of changes in previous recommendations.

Recommendation
Treatment should only be initiated in an experienced setting equipped to manage any side effects, particularly cardiovascular.
Strong recommendation in favor, level of evidence

Therapy must be initiated in ordinary hospitalization in high-risk children, also considering the compliance and socio-cultural level of the family and any comorbidities.

Question 15
To ensure greater safety in infants with infantile hemangioma and at high risk of complications from propranolol, in case of corrected age <2 months, weight <2 kg, with comorbidities, or with parents of low socio-cultural level, it is advisable to start treatment as an in-patient or in hospital?

INTERPRETATION OF THE DATA

To answer Question 15, a review of the literature was analyzed, indicating how treatment should be initiated in a facility equipped for immediate management of adverse events, *e.g.*, bradycardia. Hospitalization is necessary in cases where the patient is of a correct age <2 months and weight <2 kg, in case of inadequate social support, cardiovascular, respiratory, or glycemic control comorbidities.[14] There is consistency between the study analyzed and the expert judgment. Studies are relevant to the target population, including infantile hemangiomas that require setting detail of management in ordinary hospitalization. The proposed intervention allows for safer management of IH in patients at risk of developing adverse events, related to both comorbidities and the social context. The discomfort for the family might be linked to the hospitalization of the child. Comorbidities are the reasons for implementing the intervention hospitalization. The intervention can be carried out in reference centers equipped for assistance in the ordinary hospitalization regime of an infant.

Recommendations
To ensure greater safety in infants with infantile hemangioma at high risk of complications from propranolol, in case of corrected age <2 months, weight <2kg, with comorbidities, or with parents of low socio-cultural level, it is advisable to start treatment as an in-patient.
Point of good clinical practice

Question 16
For the treatment of infantile hemangioma, which dosage of oral propranolol is effective?

The dose of the drug is 2-3 mg/kg/day, generally divided into 2 administrations, and 3 in high-risk children. A review of the literature reports the efficacy of a dose of 2-3 mg/kg/day, for an average of 6 months of therapy, with a response of 96-98% and with complete or near complete regression in 60% of cases.[14] At these dosages it is also effective for obstructive IHs of the airways and ulcerated ones. In addition, a cohort study evaluated that the median effective therapeutic dose was 2 mg/kg/day even in patients below 5 weeks of age and above 5 months[57] and a randomized clinical trial showed a non-inferiority of propranolol compared to steroid at a dosage of 2 mg/kg/day.[56] A meta-analysis demonstrated that oral propranolol is superior to other treatments in improving IH response at a dosage of 2 mg/kg/day.[54] The American guidelines also recommend a dose between 2-3 mg /kg/day in case there are no comorbidities or adverse events that require a lower dosage S. PHACE, sleep disturbances.[12] At 2 mg, no significant differences were found in the incidence of adverse events compared to treatments with lower doses. Some adverse events occurred at doses greater than 2 m/kg/day. The 3 mg/kg /day dose must in any case be preceded by a treatment period at a dose of 1 or 2mg and may be increased in severe cases laryngeal, upper eyelid or

in case of poor response after the first month of therapy. In high-risk children, start with 1 mg/kg/day and increase after 4-7 days, if well tolerated, to 2 or 3 mg/kg/day.

INTERPRETATION OF THE DATA

To answer Question 16, a review of the literature was analyzed that reports the efficacy of a dose of 2-3 mg/kg/day, for an average of 6 months of therapy with a response of 96-98% and with complete or almost complete regression in 60% of cases. At these dosages, it is also effective for obstructive airway IHs and ulcerated ones.[14] A cohort study evaluated that the median effective therapeutic dose was 2 mg/kg/day even in patients under 5 weeks of age and over 5 months.[57] A randomized non-inferiority clinical trial demonstrated non-inferiority of propranolol compared to steroid at 2 mg/kg/day.[56] A systematic review of the literature showed that propranolol at 3 mg/kg/day compared to placebo improves clearance and median volume clinician-assessed at 24 weeks.[58]

A meta-analysis that demonstrated oral propranolol to be superior to other treatments in improving IH response at 2 mg/kg/day.[54] American guidelines recommend a dose between 2-3 mg/kg/day in case there are no comorbidities or adverse events that require a lower dose PHACE S., sleep disturbances.[12] The quality of the evidence was assessed using the Checklists for cohort studies, for randomized controlled trials, for systematic reviews and meta-analyzes and the 2016 AGREE Reporting Checklist for guidelines, with the following results: agreement on the dosage of oral propranolol. All studies agree that the best therapeutic dosage for IH is between 2-3 mg/kg/day. These studies confirm the efficacy of propranolol for high-risk IHs, compared to all other treatments. At 2 mg, no significant differences were found in the incidence of adverse events compared to treatment with lower doses. Some adverse events occurred at doses greater than 2 mg/kg/day. The intervention is acceptable considering its effectiveness in the face of scarce, transient, and controllable side effects. The intervention is feasible in the prescribing centers, present throughout the country.

Recommendations

The effective dosage of oral propranolol for the treatment of a childhood hemangioma is between 2 - 3 mg/kg/day.
Strong recommendation in favor, level of evidence 1++

The use of propranolol in PHACES S. is debated due to the risk of cerebral ischemia. However, case series treated without any complications are reported in the literature. One study analyzed the brain perfusion of children with PHACES treated with propranolol using the SPECT single photon emission computed tomography technique before and after treatment. There was no area of reduced perfusion. Therefore, it would appear that propranolol does not increase the risk of cerebral ischemia.[59]

Question 17

What is the recommended follow-up protocol for patients in systemic therapy with propranolol due to infantile hemangioma?

Regarding the follow-up protocol for patients in treatment with propranolol, the following recommendations have been imported from the previous 2015 SISAV guidelines. The review of recent literature did not reveal any evidence of changes in the previous recommendations.

Recommendations

Monthly monitoring by the treatment center for side effects with clinical evaluation and photo documentation, weight control, heart rate and blood pressure measurements is recommended.
Strong recommendation in favor, level of evidence 3

It is recommended that respiratory symptoms such as coughing, wheezing, stridor be asked at each follow-up visit.
Strong recommendation in favor, level of evidence 3

It is recommended that blood glucose is checked for abnormal sweating, irritability, malaise.
Strong recommendation in favor, level of evidence

Malaise with vomiting and diarrhea or lack of appetite should lead to temporary withdrawal of treatment.
Strong recommendation in favor, level of evidence 3

ECG monitoring and cardiac evaluation are required in case of rate <70bpm <80 in neonates or in case of auscultation or history of arrhythmia/heart disease or maternal history of connective tissue disease.
Strong recommendation in favor, level of evidence 3

In the case of diagnostic/therapeutic procedures that require fasting, intravenous administration of glucose is indicated to avoid discontinuing therapy.
Strong recommendation in favor, level of evidence 4

Propranolol requires no change in the vaccination schedule.
Strong recommendation in favor, level of evidence 4

The treatment must last at least 6 months or until one year of age. In the event of relapse, a new course of therapy can be performed.
Strong recommendation in favor, level of evidence 3

Discontinuation of treatment should not be gradual.
Strong recommendation in favor, level of evidence 4

Question 18
For the treatment of a childhood hemangioma, what time of administration with respect to meals guarantees greater safety and efficacy?

INTERPRETATION OF DATA

To answer Question 18, a systematic review and a narrative review of the literature were analyzed.[12, 14] The studies are consistent with their conclusions, all including the target population of high-risk infantile hemangiomas undergoing treatment with oral propranolol. The proposed intervention has the benefit of reducing the risk of hypoglycemia during therapy with oral propranolol. In case of administration during a meal, there is a risk that the infant will not complete the feed and may suffer from hypoglycemia. In case of regurgitation, the quantity of drug taken cannot be evaluated. The benefits of proper home management of therapy outweigh the harms. The proposed intervention can also be implemented at the patient's home.

Recommendations
For the treatment of infantile hemangioma, administration of propranolol with or after meals ensures greater safety and efficacy.
Strong recommendation in favor, level of evidence 1+

Question 19
In patients with infantile hemangiomas in whom propranolol is contraindicated, who do not respond to oral propranolol or who experience side effects, is oral corticosteroid or surgical therapy indicated for the best efficacy/safety ratio?

Oral corticosteroids

Studies agree that the oral steroid can be used to treat IH in cases where there are contraindications to treatment with oral propranolol, asthma or cardiological comorbidities, in which propranolol is not well tolerated or that does not prove effective.

The most frequently used steroid dosage is 2-3 mg/kg/day, with full dose treatment for 4-12 weeks, followed by a gradual discontinuation of therapy at 9-12 months of age. The response rate is around 35-85%. Relapses are reported in 15-37% of cases. Oral steroids are associated with iatrogenic Cushing syndrome, infections, growth retardation, hypertension, mood changes. Growth retardation is very common when therapy is started before 3 months of life or continued beyond 6 months. Use in premature babies seems to cause reduced brain growth.[60]

INTERPRETATION OF THE DATA

To answer Question 19, the American guidelines, and a review of the literature[12, 14] were used.

Studies agree that the oral steroid can be used to treat IH in cases where there are contraindications asthma or cardiological comorbidities, is not well tolerated or there is no adequate response to oral propranolol. The most frequently used dosage is of 2-3 mg/kg/day, with a TREATMENT full dosage for 4-12 weeks, following by a gradual withdrawal of the therapy at 9-12 months of age. Steroids per os association with Cushing iatrogenic, infections, growth retardation, hypertension, mood changes. Studies show a moderate degree of consistency, are relevant because they include guidelines on the target population. The benefits outweigh the risks for this surgery by adequately controlling the side effects of the systemic steroid. Side effects can be numerous and known with systemic corticosteroids. Close monitoring is important. The intervention is acceptable with adequate monitoring in reference centers with experience in the treatment of IH unresponsive to first-line therapy.

Recommendations
Oral corticosteroid indicated for the best efficacy/safety ratio.
Strong recommendation in favor, level of evidence 1+

Vincristine

It is a derivative of the Vinca alkaloids and inhibits mitosis and angiogenesis.

Question 20
What alternative drug therapy could be used in life-threatening IH resistant to propanol and cortisone, or when these two drugs have contraindications or side effects?

The following recommendation was imported from previous SISAV guidelines of 2015. Recent literature review has revealed no evidence of changes in previous recommendations. It is a derivative of the Vinca alkaloids and inhibits mitosis and angiogenesis.

Recommendations
The use of Vincristine is indicated in life-threatening IHs resistant to propranolol and cortisone, or when these two drugs have contraindications or side effects.
Strong recommendation in favor, level of evidence 3

The usual dose is 0.05 mg/kg in patients weighing less than 10 kg and 0.75-1.5mg/m^2 in those weighing more than 10 kg administered intravenously weekly for 3-4 doses. The route of administration must have a central access since the drug is a vesicant. Side effects are neurotoxicity, irritability, decreased deep reflexes, constipation, abdominal pain, paralytic ileus, cranial nerve palsy, bone pain, alopecia, myelosuppression. Nephrotoxicity is not marked in children. Treatment must be managed jointly with a pediatric onco-hematologist who monitors neurological and hematological toxicity.[61]

Topical therapy

Question 21

Is topical timolol appropriate only in the treatment of superficial, small, and thin infantile hemangioma, or also in other types of infantile hemangioma?

A systematic review of the literature analyzed a trial comparing topical timolol 0.5%, 2vv/day and placebo, used in focal, superficial IH and comparison between timolol and propranolol in the therapy of infantile and superficial IH, showing that topical timolol is more effective than placebo and comparable in effectiveness to propranolol.[62] The studies analyzed had low or very low quality of evidence. The American guidelines also report a moderate recommendation in the use of topical timolol for subtle and superficial IH.[12]

INTERPRETATION OF THE DATA

To answer Question 21, the following were analyzed.

- a systematic review of the literature, which analyzed a trial of comparison between topical timolol 0.5%, 2v/day and placebo, used in focal, superficial and of comparison between timolol and propranolol in the treatment of superficial infantile IH. Topical timolol is more effective than placebo and comparable in effectiveness to propranolol. The studies analyzed had low or very low quality of evidence;[58]
- American guidelines, which report a moderate recommendation in the use of topical timolol for subtle and superficial IHs;[12]
- a meta-analysis reporting evidence that oral b-blockers, especially timolol, may be a first-line treatment for superficial IH;[63]
- a systematic review of the literature reports that topical propranolol is useful for patients with small, superficial IH and at risk of cosmetic sequelae, in cases where the cosmetic or symptomatic impact does not require oral therapy.[62]

The evidence was analyzed using the respective checklists. The studies analyzed are consistent. The target population is superficial, small, and thin IHs. Cosmetically treat even the thinnest IHs for which oral therapy is not indicated.

Recommendations

Topical timolol is only appropriate in the treatment of superficial, small, and thin infantile hemangioma.
Strong recommendation in favor, level of evidence 1++

Laser treatment of vascular tumors

American guidelines state that pulsed dye laser PDL is effective and safe in removing residual macules and superficial telangiectasias of involuted or involutionary IHs. However, this can require numerous treatments to achieve an optimal result. Regarding the treatment of IH in the proliferative phase, numerous case reports and case series analyzed by the American guidelines report an increased risk of ulceration, scarring and residual hypopigmentation. Surgery and laser should be performed early after childhood and before school age before the development of self-esteem. [12]

Question 22

To prevent psychological distress, must residual telangiectasias be treated with laser therapy in preschool age or can spontaneous resolution be expected?

INTERPRETATION OF THE DATA

To answer Question 22, the American guidelines [12] were analyzed, which argue that PDL is effective and safe in removing residual macules and superficial telangiectasias of involuted or involuting IHs. However, this can require numerous treatments to achieve an optimal result. Regarding the treatment of IHs in the proliferative phase, numerous case reports and case series analyzed by the American LGs report an increased risk of ulceration, scarring and residual hypopigmentation. Surgery and laser should be performed early after childhood and before preschool age before the development of self-esteem. The American guidelines report consistent studies in conclusions. They are relevant and analyze the population of patients affected by IH in the involutionary or involuted phase who present visible residual telangiectasias. The goal is to avoid psychological distress in patients, in particular during school age. No damage if correctly done by experts. The operation is acceptable even if it sometimes requires sedation in younger children. The intervention is feasible in dedicated centers that have a machine such as a dye laser and the possibility of sedation in pediatric age.

Recommendations

To prevent psychological distress, residual telangiectasias must be treated with laser therapy in preschool age.
Weak recommendation in favor, level of evidence 4

Surgical treatment: indications and timing

Surgical treatment of IH is recommended in selected cases and preferably not very early in the first months of life, in which the risks related to general anesthesia, intraoperative bleeding and intrinsic to surgery are greater. In most cases, surgery is recommended at the end of the proliferative phase. In addition, cosmetic surgery has no reason to be used early, since long-term memory and self-esteem develop later in childhood, in school age. On the other hand, the early surgical option is necessary in cases where IH causes obstruction or deformity of vital structures or aesthetically involves sensitive areas, is ulcerated and unresponsive to local therapy or oral therapy. Therapy of ulcerated IH requires local dressings in combination with dye laser, infection and pain control, systemic therapy, and hemostasis.[64]

Question 23

Is deferred outcome surgery indicated in children with a vascular tumor compared to early surgery to prevent growth alterations of the involved structures?

Interpretation of the data

To answer Question 23 the following were analyzed:

- a multicenter retrospective cohort study examining the role of surgical resection after medical therapy with beta blockers and that affirms an essential role of surgery both in the case of non-responsive and in the case of partial response with the possibility of functional and aesthetic sequelae;
- a retrospective cohort study that analyzes the prevention and management strategies of disfiguring scarring of infantile hemangiomas; the study regarding surgical timing recommends early excision in cases of failure or contraindication of medical therapy, in cases of hemangiomas localized in well-defined areas and safe that do not require complex reconstructions or in cases where early intervention would lead to scarring similar to a late intervention; surgical excision must be considered in the involutional phase equally if similar scars are preceded by any subsequent surgery and if the scars are in favorable locations. In other cases, surgical removal is recommended at the end of involution;
- a retrospective cohort study of patients with hemangiomas undergoing surgical treatment, which analyzes frequency and percentage of adverse events stratified by anatomic area, size of excision, demographics and presence of risk factors and which performs multivariate logistic regression for establish the association between risk factors and adverse event; it concludes by identifying some risk factors associated with a higher rate of adverse events, including age: children under the age of 3 tend to have a higher adverse event rate. In choosing the surgical timing, it is therefore essential to take age into account;
- a systematic review of the recommendations in the management and treatment of infantile hemangioma which concludes that early surgical treatment should be considered for injuries unresponsive to medical therapy, for those that compromise vital functions and for giant injuries in light of the risk of cosmetic sequelae of the latter;
- a retrospective cohort study that globally evaluates the outcomes of various therapeutic strategies and concludes by stating that surgical therapy should be reserved for small and localized hemangiomas and for those not responsive to medical therapy;
- a retrospective cohort study that analyzes the role of the introduction of propanol, highlighting a decrease in the need for surgical excisions.[65–70]

The quality of the evidence was assessed through the checklist for cohort studies and reviews systematic with the following result: in the case of vascular tumor, early surgery is indicated in cases of non-responsiveness, partial responsiveness or contraindication to medical therapy, in cases where early intervention would determine better or similar scarring to medical therapy or late surgery especially in those involving morphological-aesthetic subunits of the face due to the associated high risk of deformity, in ulcerated focal hemangiomas and/or on hairless scalp skin, in infantile focal hemangiomas with oozing bleeding or chronic ulcers. Early surgical treatment in the indicated cases makes it possible to treat hemangiomas unresponsive to medical therapy, to ensure proper development of the structures involved and to perform the reconstruction before the child develops memory or a sense of discomfort for the deformity. The choice of a surgical approach must consider the known common risks of a surgical procedure. Early surgical therapy in the indicated cases is well accepted by family members to obtain the expected benefits. It can only be done in reference centers with specific surgical skills.

Recommendations

Early surgery in infantile hemangiomas is indicated to prevent growth alterations in the structures involved and

therefore guarantee a correct development of neighbor structures and consequently an adequate psychological development of the child in the following cases:
• in infantile hemangiomas resistant to medical therapy or with unsatisfactory response or in cases where this is contraindicated;
• in infantile hemangiomas whose early removal would lead to better scarring or similar to medical therapy or a later intervention, with particular attention to infantile hemangiomas involving morphological-aesthetic subunits of the face due to the associated high risk of deformity.
Recommendation strong in favor, level of evidence 2+

Surgery involves rare risks mostly related to general anesthesia, with permanent scars.

Scars should be placed, where technically possible, on the natural tension lines of the skin or in anatomically hidden areas. Whenever possible, surgery should be the first-choice treatment in ulcerated hemangiomas, especially if large, involving potentially disfiguring aesthetic units and if affected by complications respiratory obstructions, hemorrhages, etc. to achieve rapid healing and prevent the spread of infections. When surgery is contraindicated due to the general or local situation, advanced dressings are the treatment of choice.

Question 24
In the case of hemangioma of the scalp with probable residual imperfections alopecia, extensive ulcer, is surgical removal of the first few months of life indicated compared to medical therapy with propranolol?

INTERPRETATION OF THE DATA

To answer Question 24, the following were analyzed*:*

• a retrospective study that retrospectively analyzes a cohort of patients with infantile hemangioma of the scalp, analyzes their demographic, clinical characteristics, location, and type of treatment. He concludes by stating that hemangiomas of the scalp, especially considering the frequent complications they encounter such as alopecia 51.7% and ulceration 23.2% and thanks to skin laxity/elasticity and good healing, benefit from removal early surgery;[71]

• a study that retrospectively analyzes a cohort of patients suffering from large childhood hemangiomas of the scalp. He concludes by stating that thanks to the great scalp elasticity, early surgical removal is indicated, often in a single step, preventing the development of areas of alopecia or permanent distortion of the hairline or of the ear anatomy.[72]

The quality of the evidence was assessed using the checklist for cohort studies with the following result: agreement on early surgical treatment in cases of focal hemangioma of the ulcerated scalp and/or on hairless skin to exploit the elasticity of the scalp skin in the first months of life and achieve a rapid recovery.

Early surgical treatment provides benefits that outweigh the risks associated with a surgical procedure. The choice of a surgical approach must consider the known common risks of a surgical procedure. Early surgical therapy is an acceptable option for family members in the light of the expected benefits. It can only be implemented in reference centers with specific surgical skills.

Recommendations
In newborns with voluminous infantile hemangioma of the scalp with probable residual imperfections alopecia, ulcer scarring, surgical removal is indicated in the first months of life compared to therapy with propranolol.
Strong recommendation in favor, level of evidence 2+

Question 25
In children with infantile hemangioma of the tip of the nose and lip, after treatment with propranolol, is surgical correction at 12-18 months of life indicated compared to deferred surgery of the sequelae?

INTERPRETATION OF THE DATA

To answer Question 25, the following were analyzed*:*

• a retrospective cohort study that analyzes the association with the morphological characteristics of the hemangioma; it is concluded that during the involutional phase, hemangiomas with a deep component are at a higher risk of developing contour deformities, a factor which is therefore considered to predict the need for early surgery;

• a retrospective cohort study that evaluates the effectiveness of a specific surgical technique in correcting the outcomes of infantile hemangiomas of the lip, reporting morphologically satisfactory results of deferred surgery of sequelae;

• a retrospective cohort study that analyzes the results of surgical treatment in hemangiomas of the nose poorly responsive to medical therapy, in which a surgical management algorithm is developed based on the quality of the skin to obtain a better outcome;

• a retrospective cohort study on the management of nasal IH that provides a therapeutic algorithm which states that early surgery must be reserved to those cases that are unresponsive or partially respond to medical therapy, with a high proliferative rate or destructive.

The quality of the evidence was assessed using the checklist for cohort studies with the following result: agreement on early surgical treatment after medical therapy in cases of infantile hemangiomas of the lip or nasal tip unresponsive or poorly responsive to medical therapy, *e.g.,* high proliferative or destructive rate morphological-aesthetic elements and subunits. In these cases, surgical reduction is therefore indicated in the first months of life.[73–76] Early surgical treatment after medical therapy in selected cases provides benefits that outweigh the risks associated with a surgical procedure. The choice of a surgical approach must consider the known common risks of a surgical procedure. Early surgical therapy in selected cases is well accepted by family members considering the expected benefits. It is currently applicable only in reference centers with specific surgical skills.

Recommendations
In children with IH of the tip of the nose and lip, after treatment with propranolol, surgical correction is indicated at 12-18 months of life and a possible deferred surgery of the sequelae.
Strong recommendation in favor, level of evidence 2+

Early surgical treatment right after medical therapy in cases of IHs of the lip or nasal tip non-responsive or poorly responsive to medical therapy, with a high proliferative rate or destructive, allows a correct development of the structures involved and an adequate psychological development of the child.

Except for the cases above, the surgical treatment should be performed in the involute phase of infantile hemangioma:

- in the proliferative phase, the lesion is richly vascularized, thus determining a difficult hemostasis control;
- in the involutive phase, the surgical approach is less risky, but the extent of vascularization should be considered;
- in the involved phase, the hemangioma has a reduced or absent blood flow. Often the residual skin is redundant, dyschromic, translucent and inelastic, resembling an empty sac. Removal at this stage is relatively easy as the tumor is composed of fibroadipose tissue.

Recommendations
Except in those cases where early therapy is indicated, surgical treatment of infantile hemangiomas is recommended in the involuted phase or in the phase of involution.
Strong recommendation in favor, level of evidence 3
Surgical treatment of the sequelae must be performed before school age, preventing any psychological implications related to the distorted image of the body scheme, particularly in the case of facial hemangiomas.
Strong recommendation in favor, level of evidence 3

Question 26
Is surgical excision indicated in children with focal hemangioma ulcerated over a large part of the surface compared to advanced dressings?

INTERPRETATION OF THE DATA

To answer Question 26, a systematic review of the literature and the American guidelines were analyzed, which agree in planning and individualizing the therapeutic process of focal ulcerated hemangioma based on the site, extent, symptoms, surgical feasibility, costs, and family compliance.

Whenever possible, surgery should be the treatment of first choice in ulcerated focal hemangiomas, especially if involving potentially disfiguring aesthetic units and if affected by complications respiratory obstructions, bleeding, etc. When the general or local situation poses contraindications to surgery, advanced dressings are the treatment of choice.[12, 77] The quality of the evidence was assessed through the checklist for systematic reviews and meta-analyzes with the following result: acceptable quality +. There is heterogeneity between the methods used in the observational studies observed in the review. There is also a "publication" bias on the subject that leads to the publication of positive results, limiting the possibility of analyzing negative cases. The aim is to minimize major and minor complications of ulcerated hemangioma and achieve faster healing. The choice of a surgical approach must take into consideration the known risks common to surgery and general anesthesia. Surgery is well accepted by family members in the conditions indicated in the light of its effectiveness in terms of reduction of complications and greater speed of healing. It can only be carried out in reference centers with specific surgical and anesthetic skills.

Recommendations
In children with focal hemangioma ulcerated over a large part of the surface surgical removal is indicated compared to advanced dressings.
Strong recommendation in favor, level of evidence 1+

Congenital hemangiomas

These are fully developed hemangiomas at birth, usually single. They differ from IHs in the absence of a prolifera-

tive phase and in the histochemical negativity to GLUT-1. Three varieties are recognized: rapidly involuting congenital hemangioma RICH; non-involuting congenital hemangioma NICH and partially involuting congenital hemangioma PICH. They represent about 3% of hemangiomas and are therefore rare vascular tumors.

Epidemiology and pathogenesis

There is no apparent sex predilection. The pathogenesis is not known to date. Recent studies hypothesize an etiopathogenic role of mutations in the GNAQ and GNA11 gene with consequent hyper-activation of the MAPK and YAP angiogenic cascade.

Rapidly involutive congenital hemangioma RICH

Natural history

The RICH appears to be already developed at birth and rapidly begins its involution. In some cases, they can be identified by ultrasound in the fetal period. Regression usually completes spontaneously in the first 6-18 months of life, sometimes leaving a redundant skin similar to cutis laxa and telangiectasias. In rare cases, the involutional phase stops and takes on an appearance similar to NICH, configuring a PICH that tends to persist unchanged over time.

Clinical Aspects

Clinically, 3 morphological variants of RICH are distinguished:

- vascular lesion of red-purpuric color, with gross telangiectasias on the surface;
- scarcely detected red-violet plaque and telangiectasias;
- vascular swelling of grayish color with fine telangiectasias surrounded by a pale halo.

Elective locations are the limbs, especially near a joint, the head and neck. Possible complications are hemorrhage, transient and self-resolving thrombocytopenia and ulceration that usually appears in the center of the lesion and at the beginning of the involution phase. [78]

The follow-up is necessary in the regression phase with periodic clinical and laboratory checks platelets, D-dimer, fibrinogen, and degradation products of fibrinogen.

Diagnosis

Diagnosis is essentially clinical. Its differential diagnosis is with fibrosarcoma, rhabdomyosarcoma, Kaposiform hemangioendothelioma, tufted angioma, cystic hygroma and teratoma. In some cases, it is necessary to resort to instrumental and/or histological investigations.

Question 1
In a patient with suspected Congenital Hemangioma, are physical examination and anamnesis sufficient compared to further diagnostic investigations in order to guarantee a correct diagnostic classification?

INTERPRETATION OF THE DATA

To answer Question 1, four case reports were identified in the literature that considered patients with congenital hemangiomas. The latter reported the importance of imaging in particular ultrasound for a correct evaluation and differential diagnosis, in particular for visceral forms without skin compensation.[24, 79–81]

The conclusions of the analyzed studies are consistent with each other to a high degree. There is concordance of outcome and validity of the instrumental method for diagnosis, which is fundamental in addition to the clinical approach. The benefit of the recommendation is to carry out a better assessment of congenital hemangioma and suspected such by ensuring better differential diagnostics through non-invasive methods primarily ultrasound and by analyzing both superficial and deep tissues. The impact on the patient is minimal, as it is a non-invasive assessment. The feasibility is good in the entire national context. Being operator-dependent, it should be performed by experienced personnel. The studies reviewed are relevant to the target population, include cutaneous and visceral congenital hemangiomas and an assessment on subjects similar to those to whom the key Question is addressed.

Recommendations
In case of suspicion of congenital hemangioma, in addition to the correct medical history, color Doppler ultrasound is recommended as a more appropriate and non-invasive instrumental diagnostic approach.
Weak recommendation in favor, level of evidence 3

Congenital non involutive hemangioma NICH

Clinic

Clinic NICH is already present at birth with a warm lesion, flat in 30% of cases and nodular or plaque in 70% of cases, ranging in color from red to bluish white surrounded by a peripheral whitish halo. The surface is often furrowed with coarse telangiectasias and with evident ectatic veins in the periphery. Elective sites are the trunk and the lower limbs; less frequently it involves the head and neck. The course is characterized by a growth proportional to physiological growth and puberty. Peripheral veins may become more noticeable. In some cases, pain is reported.

In some cases, it is necessary to resort to instrumental and/or histological investigations. [82]

Partially involutive congenital hemangioma PICH

It manifests itself with a clinical and radiological aspect typical of RICH, with rapid involution in the first year of life and slower in the further 2-3 years. However, it does not completely regress and assumes NICH-like characteristics. [83]

Question 2
Is a histological/molecular investigation always necessary in a patient with suspected Congenital Hemangioma compared to clinical-instrumental evaluation alone to ensure a correct diagnostic classification?

INTERPRETATION OF THE DATA

To answer Question 2, four case reports/series were identified in the literature which considered patients with congenital hemangiomas, and which reported the presence of some histological and genetical feature that characterize them. The studies showed the absence of validated genetic methods to distinguish congenital hemangiomas from each other as well as innovative markers for histological investigation the only element of distinction remains the well-known negativity of GLUT1 compared to IHs underline the predominant role of imaging for correct evaluation and differential diagnosis.[81, 84–86]

The conclusions of the studies analyzed are moderately consistent with each other. The studies are relevant to the target population, include cutaneous and visceral congenital hemangiomas as well as an evaluation of histology and genetic methods compared to those of images. The studies show a better usability and diagnostic evidence of the instrumental method compared to invasive methods. The benefit of the recommendation is to avoid resorting to biopsy investigation in cases that would benefit more from imaging methods. The use of histology should be limited to those cases where the imaging methods are unable to provide a description sufficient for the diagnosis. To date, genetics does not guarantee important diagnostic turning points. Where invasive investigations are used, coordination with a reference center for histochemical and genetic analyzes is necessary.

Recommendations
In the suspicion of congenital hemangioma, non-invasive imaging is always recommended as the first line to complement the clinical approach rather than a histological/molecular study, to ensure a correct diagnostic framework.
Weak recommendation against, level of evidence 3

Congenital hemangioma with prenatal presentation

The finding of Congenital Hemangiomas at fetal ultrasound examinations is occasional and often related to bulky hemangiomas. To monitor the size of the hemangioma and any associated complications over time, serial controls by ultrasound play a fundamental role. If these forms were found at an antenatal level, a multidisciplinary evaluation gynecologist, pediatric neonatologist, dermatologist, pediatric surgeon, vascular surgeon would be advisable in addition to a thorough imaging investigation to better manage possible intrapartum and neonatal complications.

Question 3
In a fetus with suspected prenatal congenital hemangioma, is an in-depth imaging evaluation and a multidisciplinary approach necessary compared to a simple ultrasound follow-up in order to guarantee a correct diagnostic classification?

INTERPRETATION OF THE DATA

There are no adequate studies to evaluate the evidence study of the role of multidisciplinary evaluation in the management of congenital hemangiomas with prenatal finding.

Recommendations
In the case of a congenital hemangioma with prenatal diagnosis, to guarantee a correct diagnostic framework and adequate clinical management, an imaging evaluation and a multidisciplinary approach are recommended compared to the simple mono-specialist ultrasound follow-up.
Point of Good Clinical Practice.

Therapy of congenital hemangiomas

RICH generally does not require any treatment, due to the possible rapid involution. Treatment is necessary for residuals of RICH, PICH and NICH. The therapy is embolization and/or surgery; it is indicated in early childhood, before the onset of awareness of one's own body image, or in adolescence when the patient will be able to decide independently. In case of excessive subcutaneous atrophy, autologous grafts fat, dermis or acellular dermis can be used. Residual telangiectasias can be managed with the pulsed dye-laser.

Question 4
In a patient with suspected congenital hemangioma in the presence of functional deficits and/or possible serious aesthetic outcomes, is an active intervention necessary compared to an observational follow-up to guarantee the best possible quality of life and complete resolution?

INTERPRETATION OF THE DATA

To answer Question 4, three case reports were identified in the literature that considered patients with congenital hemangiomas accompanied by severe functional or aesthetic deficits. In some of these, particular emphasis is given to the minimally invasive therapies that can be used in particular endovascular, in addition to the well-known surgical and laser therapies guaranteeing excellent results both at the vascular and aesthetic-functional level.[79, 87, 88]

The conclusions of the analyzed studies are consistent with each other to a moderate degree. There is agreement of the interventionist method to achieve a good outcome. Ensuring a better outcome of congenital hemangioma in those patients suffering from highly impacting forms at a functional and/or aesthetic level. In relation to the type of method, there are various connected risks, from anesthetic to surgical ones, and for this reason the recommendation is limited to patients with severe functional and/or aesthetic deficits. In relation to these indications and the excellent results associated with invasive methods, the risk/benefit ratio is in favor of the patient. Reference structures with experienced personnel are needed in the treatment of these lesions using the most recent and innovative methods. At the territorial level there are already specialized structures, and it is advisable to direct patients towards these realities.

Recommendations

In a patient with suspected congenital hemangioma in the presence of functional deficits and/or possible serious aesthetic outcomes, active intervention is recommended using interventional techniques embolization, surgery, laser therapy to ensure a better quality of life and complete resolution compared to a simple observational follow-up.
Weak recommendation in favor, level of evidence 3

Hemangioendothelioma and tufted angioma

Kaposiform hemangioendothelioma KHE and tufted angioma TA are now considered by some experts in the field as a spectrum of the same rare vascular tumor with borderline behavior characterized by local progression and systemic symptoms. These are rare vascular tumors that typically arise in childhood. Many experts argue that they are part of the same neoplastic spectrum.[89] KHE has borderline behavior, is characterized by local aggression, and can be complicated by systemic symptoms of which the most serious is the Kasabach-Merrit phenomenon KMP. TA has a tendentially benign course, KMP has rarely been observed in patients with this tumor.

Pathogenesis

The etiopathogenesis, to date, is not yet fully understood and it is probably linked to an alteration of the mechanisms of regulation of angiogenesis and lymphogenesis; neoplastic cells express both markers of the vascular endothelium CD31, CD 34, VEGFR-3 and of the lymphatic endothelium D2-40- podoplanin, LYVE1 and PROX1 Table I.

Kaposiform hemangioendothelioma

Epidemiology

Kaposiform hemangioendothelioma is a rare, locally aggressive, vascular tumor, with very low metastatic potential. Its incidence and prevalence are estimated at 0.91 and 0.07/100,000 children per year respectively, [90] but they are underestimated as asymptomatic and small lesions and are sometimes classified as variants of infantile hemangioma or other vascular anomalies. It occurs in 93% of cases during childhood, 60% in infants.[91] Two retrospective studies show a slight predilection for the male sex. There is no predilection for race.[90]

Clinical aspects

The localization of the KHE can be cutaneous and extracutaneous. Usually, the cutaneous form of KHE appears as a red-bluish vascular swelling, superficial or deep, varying in size from a few cm up to involving an entire limb, hard and not compressible to the touch.[90] The lesion can affect the skin and subcutis up to the fascia, muscle and sometimes bone. Locations of choice are the trunk and extremities, more rarely the head and neck. The most affected anatomical sites are the limbs, the trunk, the head, the neck, the retroperitoneal region, the mediastinum, the internal organs, the bones, and the joints.[92] Localizations in the extreme cephalic and retroperitoneal region are more common in infants.

KHE morphologically can be classified into:

- superficial dermis, subcutaneous, deep fascia;
- mixed skin, muscle, mediastinum, retroperitoneum;
- deep non-skin lesions, retroperitoneum, mediastinum, internal organs, bones, joints.

Diagnosis

Diagnosis is based on agreement between clinical data, radiological and histological examinations.

Laboratory tests are essential for the diagnosis and monitoring of KMP.

Prognosis

Small tumors <5 cm appear to have a better prognosis due to the low risk of complications such as KMP. The risk

of rapid growth, development of systemic symptoms and poor prognosis are more common in patients less than 5 years of age. The retroperitoneal location is the one with the highest risk of KMP. Larger tumors have an increased risk of association with KMP. KMP is reported in about half of the cases and is characterized by consumption coagulopathy by entrapment of platelets in the tumor and sometimes leads to exitus. In all cases, a check of platelets, clotting test, D-dimers, fibrinogen must be performed. It can regress in the first two years of life. KHE is a vascular neoplasm with a low degree of malignancy, locally aggressive due to its tendency to infiltrate the surrounding tissues but with a low metastatic potential, especially to the regional lymph nodes. Distant metastases are exceptional. 10-30% of cases die from complications related to the tumor or the KMP.

Tufted angioma

Epidemiology

TA is a benign vascular tumor that occurs in the first 5 years of life, 50% of cases in the first year of life. Congenital TAs are between 54-78% of cases. There is no predominance of sex.[89]

Clinical aspects

It typically appears as a solitary lump or dark red or purplish infiltrated plaque, fixed, with faded margins. The dimensions vary from 1 to 10 cm in diameter. The common localization is in the limbs, face, trunk. It can rarely involve the oral cavity mucous membrane. The overlying skin may present with hypertrichosis and hyperhidrosis. It is characterized by a slow growth phase and a stabilization phase, followed by a spontaneous, partial, or complete regression, which occurs in the first two years of life. However, there are cases with a protracted course. Careful follow-up is necessary especially in early childhood, due to the risk of complications such as KMP. The TA shows no predilection of race or sex. It is congenital or acquired with onset usually within the first 5 years of life. Although originally described in young adults, it actually occurs more commonly in the prepuberal age. The lesion tends to grow slowly and then stabilize. Spontaneous regression is possible and occurs in the first two years of life. However, there are cases with a protracted course. Although malignant transformation of the tumor has never been reported, careful attention and follow-up are required especially in early childhood, due to the risk of complications such as KMP.

Diagnosis

Diagnosis is based on agreement between clinical data, radiological and histological examinations.

Laboratory tests are essential for the diagnosis and monitoring of KMP.

Prognosis

The prognosis is better for congenital AT and for those that manifest in the first year of life, so a "wait-and-see" approach should be the initial option. Partial or complete spontaneous regression was reported in 61.54% of congenital TA cases.[89] The most common sequelae are atrophy, telangiectasias, pigmentation abnormalities. The most common outcomes of TA and in particular of KHE are fibro-atrophic with musculoskeletal dysfunction, pain, lymphedema, compression of vital organs, and death occurs in 10-30% of cases.

Kasabach-Merritt phenomenon

Seventy percent of Kaposiform Hemangioendothelioma KHE cases and 10% of Tufted Angioma TA cases can be complicated with Kasabach-Merrit Phenomenon KMP, a life-threatening thrombocytopenic coagulopathy. The particular histological structure of these tumors KHE and TA can determine the adhesion, sequestration and activation of platelets followed by consumption coagulopathy. Clinically, KMP should be suspected if the tumor has rapid growth, pain and/or purpura appears. If KMP is suspected, platelet counts, D-dimer and fibrinogen measurements must therefore be performed. Thrombocytopenia can be severe with PLT values below 5000, fibrinogen can be significantly decreased, d-dimer can be increased, while clotting test might be normal or mildly elevated. A secondary anemia might be found due to intralesional hemorrhage caused by thrombocytopenia and/or the hemolysis of red blood cells in the tumor structure. The risk of coagulopathy is higher in patients under the age of 1-5 years 79% in patients under the age of 1 year, 47% between 1-5 years, in those with a large tumor 75% in patients with tumors >82 cm^2, in the retroperitoneal forms, in the multifocal forms or in those with tumor that has passed the onset site. In these situations, early therapeutic intervention is suggested embolization, surgery, etc.

Question 1
In children with suspected Kaposiform hemangioendothelioma, which radiological tests are accurate for a correct diagnostic classification?

For aggressive and/or malignant vascular tumors, imaging diagnostics is always required, second-level diag-

nostics, for the purpose of assessing the extent of the disease, involvement of contiguous anatomical structures and potential metastases.[15, 16, 18] On ultrasound examination, kaposiform hemangioendotheliomas KHE appear as lesions with an inhomogeneously hyperechoic echostructure, blurred margins, intense and heterogeneous vascularization supported by deep vascular peduncles, multi-compartmental involvement and "stranding" in the adjacent deep subcutaneous adipose tissue or in the soft tissues and associated with skin thickening. Although ultrasound may suggest the hypothesis of KHE, a more specific diagnosis can be obtained through MRI which can better highlight its extension and infiltrative aspect. Ryu reports three distinct morphological patterns for KHE: well-defined solid mass, central solid mass with surrounding infiltrative areas, and infiltrative lesion without central solid area.[93] For the purpose of the differential diagnosis with other vascular tumors and in particular with hemangiomas, in addition to the infiltrative pattern, the other findings are: signal variability in T1W iso-hyperintensity in T1W and especially in T2W iso-hypointensity or mild inhomogeneous hyperintensity in T2W due to deposits of hemosiderin or intralesional hyaline stromal matrix, heterogeneous enhancement after contrast – probably in relation to the presence of abnormal intralesional thin-walled lymphatic vessels – and destruction/remodeling of the adjacent bone. In diffusion sequences, lesions are mildly hyperintense with low ADC. Hu reports that diffuse infiltrative subtypes of KHEs are more associated with Kasabach-Merritt phenomenon and reticular lymphedema than with solitary lesions.[93, 94]

Recommendations
MRI is indicated as the imaging method of choice for framing KHEs.
Strong recommendation in favor, level of evidence 3

Treatment

Question 2
In patients with inoperable KHE, can the combination of systemic steroid and vincristine be considered a first-choice therapy compared to that with steroid alone or vincristine to achieve tumor reduction or resolve KMP?

To date, there is no approved therapeutic protocol. Treatments range from simple observation for small lesions, to surgery, to common medical therapy with steroid, vincristine, ticlopidine, plasma-supported interferon, cryoprecipitates, and sirolimus.

INTERPRETATION OF THE DATA

To answer Question 3, four articles have been identified in the literature: one consensus, two meta-analyzes and a retrospective review.[95–98] Systemic steroid treatment prednisone 2 mg/kg/day orally or methylprednisolone 1.6 mg/kg/day iv, in the 2013 consensus, was indicated as first-line treatment for KHE/TA patients without KMP and the steroid-vincristine combination as first-line therapy for the treatment of KHE associated with KMP.[95] The steroid was administered for 3-4 weeks, until hematological parameters normalized, and the vincristine was administered for 20-24 weeks. Although systemic steroid therapy has been used and considered first-line in the treatment of KHE/TA for years, there have been reports of poor monotherapy response, relapses to suspension or even resistance to it.[96, 99] Vincristine was considered an excellent therapeutic choice in these cases. In the meta-analysis of Liu *et al*., vincristine was compared 0.05 mg/kg iv week, as well as to steroid therapy, to other treatments interferon α, radiotherapy, embolization, aspirin/ticlopidine and sirolimus in KHE/TA patients with/without KMP. Vincristine was relatively more effective, gave fewer side effects and better outcomes than the systemic steroid prednisone 2 mg/kg/day orally or methylprednisolone 1.6 mg/kg/day i.v., so it could be considered the drug of first choice. The best results were obtained for patients <3 years old in whom fewer complications were observed than in older patients, strongly supporting the need to start therapy early.[97] In the retrospective review by Schmid *et al*. in 2018, the effect of the steroid and vincristine on mass reduction and the KMP phenomenon was analyzed in monotherapy or in combination. Vincristine gave better results on both mass reduction and KMP.[98]

Recommendations
Treatment with vincristine and steroid in patients with unresectable KHE with or without KMP is recommended.
Strong recommendation in favor, level of evidence 1+

Question 3
For patients with non-removable KHE in growth or progression, treatment with Sirolimus *versus* systemic steroid and/or Vincristine can be considered first choice therapy?

INTERPRETATION OF THE DATA

To answer Question 3, six articles were considered.[90–92, 98, 100, 101] In the last decade, numerous cases of KHE patients treated with sirolimus have been published. The dose used was of 0.8 mg/m2/dose, 2 times a day, keep-

ing blood levels between 8-15 ng/mL. Sirolimus has been shown to be effective and safe in patients with progressive, symptomatic KHE with dramatic growth, functional impairment, and/or presence of KMP 40% already treated with other drugs with insufficient response.[92] The steroid was paired in the presence of KMP or compression symptoms and gradually discontinued after an average of 7.2 weeks. Therapy was continued with sirolimus alone. There were not significant differences between those treated with steroid plus sirolimus compared to those treated with sirolimus alone. Both clinicians and parents preferred this association to vincristine plus steroid as it avoided venous access placement. In the review written by Schmid, sirolimus compared to the steroid as well as vincristine and interferon alfa gave a better response on both KMP and mass reduction.[98] In Wang's 2019 work, patients with and without KMP already treated with other drugs steroid, vincristine, propranolol, interferon, and sclerotherapy who had not responded or relapsed were treated only with sirolimus with effective response and few side effects.[91] In the JI 2020 review, sirolimus plus steroid combination is considered, to be the first line of treatment in KHE patients with KMP and more effective than monotherapy in severe forms of KMP.[90] At the moment, however, there are no prospective randomized studies to define the association sirolimus plus steroid as the first-choice treatment. However, sirolimus is also effective when used alone and the insertion of the steroid must be evaluated on a case-by-case basis. The therapy of complicated or progressive KHE and TA with Sirolimus has a strong recommendation in favor, however the indication will be evaluated on a case-by-case basis. In patients with progressive or complicated KHE, treatment with the steroid plus sirolimus compared to Sirolimus has a weak recommendation in favor and a level of evidence 2+.

Recommendations

Sirolimus therapy is recommended for complicated or progressing KHE and TA.

Strong recommendation in favor, level of evidence 2+

Question 4

In patients with superficial TA/KHE, can topical therapy with tacrolimus be considered compared to the "wait and see"?

INTERPRETATION OF THE DATA

To answer Question 4, three articles[90, 102, 103] were analyzed. The clinical heterogeneity of KHE and TA justifies the need to identify a less invasive therapeutic path, compared to the systemic drugs mentioned above, for superficial or circumscribed forms, where surgery is not indicated, which present progression and/or superficial invasiveness. The evolutionary risk of the wait and see of these lesions is however towards atrophic sclero outcomes. Tacrolimus 0.1% ointment applied twice a day to superficial KHE/TA lesions represents an effective and safe therapy applied for 12 months. The result is a reduction in edema and fibrous outcomes.[103] The rationale for its use is represented by inhibitory activity on angiogenic factors including VEGF, fibroblast growth factor and IL6. The safety profile of the topical calcineurin inhibitor and its efficacy also in the pediatric patient is proven for inflammatory pathologies with fibrotic evolution.[103] Further prospective and multicenter randomized studies are needed to recommend its use in this context.

Recommendations

Topical treatment with tacrolimus for superficial TA/KHE is indicated instead of observation.

Weak recommendation in favor, level of evidence 3

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Guidelines for capillary malformations

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Introduction

Definition

Capillary malformations (CM) are low-flow vascular anomalies that are localized in the skin and mucous membranes and present as congenital spots ranging in color from pink to red-purple, histologically characterized by the presence of a dense network of blood vessels of small size (proper capillaries and post capillary venules), abnormally and permanently dilated and located in the contest of the papillary and reticular dermis of the skin and mucous membranes.

CMs can be isolated or in association with other congenital anomalies in the context of complex polymalformative syndromes, described in the chapter dedicated.[1-3]

Classification and nomenclature

The 2018 ISSVA Classification is reported, in which various syndromes are listed as subheadings included in the chapter of capillary malformations.

Only pure capillary malformations (CM) will be considered here (Table I).

CM nomenclature is quite confusing. The widely used term "plane angioma" is a source of ambiguity and should be abolished.

Two main forms can be distinguished.

Table I.—*Capillary malformation.*

Cutaneous and/or mucosal CM (also known as "port-wine" stain)
CM with bone and/or soft tissues overgrowth
CM with CNS and/or ocular anomalies (Sturge-Weber syndrome) G
CM with arterovenous malformartion
CM of MIC-CAP (microcephaly-capillary malformation)
CM of MCAP (megalencephaly-capillary malformation-polymicrogyria)
Telangiectasia
HHT: Hereditary hemorrhagic telangiectasia
Cutis marmorata telangiectatica congenita (CMTC)
Nevus Flammeus Neonatorum (Nevus simplex / Salmon patch / "angel kiss", "stork bite")
Others

Medial congenital capillary macula

Synonyms: nevus flammeus neonatorum, nevus simplex, "salmon patch" or "fading capillary stain" or medial telangiectatic nevus in Anglo-Saxon terminology.

Extremely common in the Caucasian race, clinically it presents as a skin macula evident at birth, of a pink-red color that yields to vitropressure, possibly associated with fine telangiectasias and characterized in most cases by a progressive spontaneous resolution during the first years of life.

The most commonly affected anatomical sites are found along the midline of the body:

- The nape and occipital region ("stork bite"): in this case it tends to persist into adulthood;
- Forehead, glabella, upper eyelids ("Unna's nevus," or "angel's kiss"). The sacral region ("butterfly mark") is less affected, while the lesion may be single in the medial site or there may be more spots randomly arranged on the back.

The medial fronto-facial CM is a particular and sometimes familiar form of salmon patch that affects the midline of the face (forehead, glabella, upper eyelids, nose, upper lip) of an intense red color similar to a PWS. A forehead and glabellar CM, which are always affected, can variably be associated with one or more patches along the median line. It differs from the salmon patch by its slower and often incomplete resolution. No extracutaneous anomalies are associated.[1]

Lateral congenital capillary macula

Synonyms: Port wine stain-PWS in Anglo-Saxon terminology; nevus flammeus or lateral telangiectatic nevus.

It appears at birth as a rosy-red or port-wine stain, of variable size and with sharp edges; it yields to vitropressure.[4-7]

Question 1
Is it necessary to distinguish between congenital medial capillary macula and lateral congenital capillary macula?

Recommendation of good clinical practice, based on the experience of the panel: GGP grade. It is no supported by

scientific evidence due to the absence of studies in literature.

Recommendations

The lateral congenital capillary macula must be differentiated from the medial congenital capillary macula, a benign form that is not associated with other pathologies and does not require further investigations.

Recommendation of good clinical practice, based on the experience of the panel: GPP grade

Epidemiology

CMs represent the most common form of vascular malformation, with an estimated incidence in the general population of 0.3%, excluding congenital medial capillary macules.

The distribution between the sexes is equal. They are potentially ubiquitous, but most of them are found in the extreme cephalic region (57% in the central-facial region) and 85% are unilateral, located in a dermatomeric distribution. [1-3]

Etiopathogenesis

CMs are caused by an error in embryonic development that affects the development of an abnormal number of capillary vessels in the dermis or by a normal number of capillary vessels which result permanently dilated.

They are mostly sporadic but rare familial forms with autosomal dominant inheritance with incomplete penetrance and variable expression have also been reported.[8]

Several etiopathogenetic mechanisms have been hypothesized:

• the capillaries' ectasia could be caused by a lack of neuronal control of the vascular tone. Immunohistochemical studies have shown a smaller number of nerve fibers associated with the ectatic capillaries of the CM;[9-10]

• the over-expression of VEGF and its receptor, which are increased;[11]

• the somatic mutation of the GNAQ gene is observed in patients with CMs and Sturge-Weber Syndrome (SWS). [12] Isolated or non-syndromic CMs could represent the result of a later somatic mutation in vascular endothelial cells, while in SWS an earlier mutation would involve a precursor progenitor and could be responsible for the overall neurocutaneous syndrome. Furthermore, more recent studies have shown the existence of one genotype-phenotype correlation highlighting how the p.Arg183Gln mutation of the GNAQ gene is strongly associated with CMs of the superior region of the face and with SWS. [13] More recently, a somatic mutation of the GNA11 gene has been identified in patients with CM associated with overgrowth of the involved limb;[14-15]

• the germinal or post-zygotic mutation of the PI3K / AKT / mTOR pathway has been identified in patients with Klippel-Trenaunay syndrome, with CLOVES syndrome (Congenital, Lipomatous, Overgrowth, Vascular malformation, Epidermal Nevi and Spinal / Skeletal anomalies and / or Scoliosis), with diffuse capillary malformations and hypertrophy (CMO, capillary malformation with overgrowth), and with capillary malformation syndrome - megalencephaly - polymicrogyria (MCAP) and in other conditions belonging to the PIK3CA-Related Overgrowth Spectrum (PROS);[16-19]

• mutations in the RAS-MEK-ERK and RAS-AKT-mTORC1 pathways are involved in the pathogenesis of some MCs associated with arteriovenous malformations.

The RAS family of genes is involved in the regulation of cell proliferation and differentiation and in the organization of endothelial cells.[20]

Based on the type of mutation, two CM phenotypes associated with arteriovenous malformation have been identified: the CM-AVM1 phenotype associated with various mutations of the RASA1 gene, and the CM-AVM2 phenotype associated with the EPHB4 gene mutation and characterized by the presence of labial and perioral telangiectasias. The latter phenotype shares clinical manifestations common to CM-AVM1 and hereditary haemorrhagic telangiectasia.[21, 22]

Clinical presentation

CMs are evident on physical examination as persistent vascular spots that yield to vitropression, ranging in color from pink to vinous red. The affected skin does not show an increase in heat.

CMs can manifest themselves in any body site with a preference for the face, where they often assume a "mosaic" or quadrant distribution, like a metameric distribution according to the segmental distribution territory of the embryonic vascularization.[23] In this case, the CM can be single or multiple, mono or bilateral. Extension to mucous surfaces is also possible. The distribution of CM to the upper quadrants of the head may represent a sign of a SWS in which leptomeningeal and ocular involvement is observed. SWS is the result of a somatic mutation and the risk does not correlate with the localization of the CM along the distribution territory of the trigeminal nerve but with the hemifacial, frontal or median localization.

For other sites in the absence of neurological signs

or symptoms, clinical follow-up is recommended. For screening, see the specific chapter.[24, 25]

At the lower limbs the CMs sometimes have a geometric border with a geographical aspect.

In this case, the suspicion of a complex malformative pathology is very high. Physical examination and Doppler ultrasound are important for diagnosis. Therefore, overgrowth and venous or lymphatic malformations, typically associated, must be investigated.[26]

The trunk can have a homogeneous appearance, variable shape, and color that varies from pink, red to vinous red, and be present in variable numbers. On the other side, the CMs may have diffuse reticular aspect.

CMs with geographic distribution, with a geometric border located in the lower limb, and with possible extension to the trunk, are more frequently associated with complex malformations, affecting the arteriovenous and venous districts. Round-shaped, homogeneous rosy-colored CMs surrounded by an anemic halo most often affecting the trunk and limbs are the typical presentation of a CM associated with capillary malformation-arterovenous malformation (CM-AVM). The diffuse reticular form that affects multiple contiguous body segments in a uni- or bilateral way can be associated with overgrowth of the affected area in the context of the PIK3CA-related Overgrowth Spectrum (PROS) polymalformative syndromes.

Furthermore, a careful objective examination of the entire skin area must be carried out to look for the presence of asymmetry, usually due to the overgrowth of a segment or hemibody, anomalies of the fingers (syndactyly, "sandal gap", macrodactyly), macrocephaly, other associated bone and neurological abnormalities. Another important aspect to investigate is the familiarity.[27-29]

Typically, a CM is already present at birth and persists throughout life, increasing on the surface in proportion to body growth. At birth they often have a purplish-red color due to the high hemoglobin content in the skin capillaries in neonatal age or to the phenomenon of vasoparalysis. This chromatic intensity naturally fades during the first months of life.

Unlike the medial congenital capillary macula (salmon patch or nevus simplex), which does not reflect a cutaneous mosaicism for which it can undergo resolution over the years and is not associated with syndromes complex malformations,[30] lateral congenital CMs or PWSs can assume a purpuric-red color over the years due to the increase in the density of capillaries in the dermis and the persistence of ectasia of the vessels themselves with consequent stasis. As mentioned, CMs can present a "geographical map" distribution, more frequently in association with complex malformative syndromes which will therefore be investigated.[31]

Sometimes the skin affected by CM presents in adulthood a hypertrophic-nodular evolution with progressive thickening and appearance on the surface of nodules with an appearance defined as "cobblestone." It is believed that this evolution is due to the proliferation of the vessels with their surrounding stroma and the nervous alteration of the blood flow due to a progressive deficit of the autonomic system with consequent deregulation of the vascular tone.[32]

Furthermore, lateralized forms can be associated with hypertrophy of the affected area: when localized to a half face (involving the cheek, chin and lip), they can cause hypertrophy of the soft tissues, mucous membranes and skeleton corresponding to the maxillofacial hemidistrict (CM often extends from the cutaneous to the mucous area). When localized to the limbs, they can be associated with hypertrophy and/or hypermetry.

Recent studies have shown that this hypertrophy is not only found in syndromic forms, but also in isolated forms of CM; the preferred location is the face and the average age of onset is 31 years.[32, 33]

Clinical variants

The acquired form of CM was firstly described in 1939 as Fegeler's disease. The age of appearance varies from 3 to 69 years, the most involved sites are the cephalic extremity and the upper limbs. The acquired form is usually limited to the skin. The histological examination shows a typical picture of CM. Although the etiology is not known, a traumatic event is associated in about one third of cases. Unlike the congenital form, somatic tissue mutations of PIK3CA are reported only in a pediatric case of acquired CM associated with overgrowth of the affected limb. Pulse dye laser is the most often used treatment, although the result is variable.[34, 35]

Acquired forms of PWS-like enter into differential diagnosis with linear morphea in the initial inflammatory phase and with tufted angioma with minimal infiltrative component.[36, 37]

Question 2
Quali sono gli aspetti caratteristici della malformazione capillare? What are the characteristic aspects of capillary malformation?

Question 3
What are the clinical characteristics useful in order to distinguish the isolated form the complex forms?

Question 4
Is long-term follow-up necessary in isolated capillary malformations?

Recommendation of good clinical practice, based on the experience of the panel: GGP grade. It is no supported by scientific evidence due to the absence of studies in literature.

Recommendations
Question 2: Clinical evaluation of the shape, color, location, and number of lesions is essential for the characterization of the capillary malformation.
Recommendation of good clinical practice, based on the experience of the panel: GPP grade

Question 3: The morphological characteristics and the site, together with the presence of associated signs, are important for the distinction between isolated forms of capillary malformation and complex malformative syndromes.
Recommendation of good clinical practice, based on the experience of the panel: GPP grade

Question 4: Isolated capillary malformations require prolonged follow-up for the possible evolution of the hypertrophic-nodular type or for the association with hypertrophy of the soft tissues, mucous membranes and skeleton of the involved area.
Recommendation of good clinical practice, based on the experience of the panel: GPP grade

Teleangectasias

Telangiectasias are dilations of small cutaneous or mucous vessels visible to the naked eye. They present a linear, reticular, pointed or stellar shape. Unlike purpura, they disappear on acupressure. The number of lesions varies from a few units to multiple forms, sometimes scattered.

Unilateral nevoid telangiectasia and hereditary benign telangiectasia with diffuse lesions are distinguished among the multiple element forms; both are limited to the skin. Hereditary hemorrhagic telangiectasia (HHT), also known as Rendu-Osler-Weber disease, is a complex pathology that presents with mucocutaneous telangiectasias especially on the face, lips and hands, associated with recurrent nosebleeds which are the first sign that guides the diagnosis, and visceral hemorrhages due to pulmonary and gastrointestinal arteriovenous malformations (see the chapter on syndromic forms).[30]

Diagnosis

Clinical aspect

The diagnosis of CM is essentially clinical. Comprehensive physical examination and in-depth diagnostic tests are useful in differentiating isolated and syndromic forms.

Dermoscopy is a useful non-invasive diagnostic aid that allows both the diagnosis in doubtful cases and the evaluation of the response to laser treatment.

In fact, CMs can rarely simulate an infantile hemangioma during the prodromal phase. However, in the case of CM, dermoscopy will highlight the following aspects: in superficial CM forms (or of the papillary dermis) the vessels have a punctiform or globular appearance and are oriented in a vertical direction, while in deep CMs (or of the subpapillary dermis) the vessels appear linear as they are oriented in a horizontal direction.[38, 39]

The instrumental evaluation must fundamentally distinguish the pure capillary forms from the mixed capillary-venous forms and exclude the possible presence of congenital arteriovenous fistulas present in the capillary-arteriovenous forms.

Verrucous angiokeratomas have to be considered mixed capillary-lymphatic forms.

Question 1
Is clinical characterization sufficient in the diagnosis of capillary malformation or are additional diagnostic tools required?

The following recommendation is of good clinical practice and based on the experience of the panel. It is not supported by scientific evidence due to the absence in the literature of studies concerning the specific question.

Recommendations
The diagnosis of capillary malformation is clinical; dermoscopy represents an important diagnostic and predictive aid for the response to laser treatment.
Recommendation of good clinical practice, based on the experience of the panel: GPP grade

Histology

CMs have a common histological aspect, although they may have different clinical features.[40] They can be present in syndromic patterns, and can be isolated or combined with other types of vascular malformations. [30] CMs are most frequently found in the skin, in the papillary and reticular dermis, and more rarely extend to the subcutaneous tissue. The malformed vessels are small in size, of the capillary/post-venular type, with a higher density than the surrounding tissue. Their lumen is ectatic, rounded and occupied by red blood cells; the wall is thin and consists of a single layer of flat endothelial cells, without atypias and mitotic activity, resting on the basal membranes sur-

rounded by occasional pericytes. The pericytes increase in number going towards the post-capillary venules and are associated with some smooth muscle cells. Over the years, the vascular wall tends to thicken and become fibrous.[40-42]

The verrucous venulo-capillary malformation (verrucous hemangioma) is a CM variant with histological characteristics that vary over time due to a progressive epidermal orthokeratotic hyperkeratosis. This CM is limited to the papillary dermis, sparing the reticular dermis and has capillary / venular vessels in the subcutis, often grouped. In addition to widespread positivity for the immunocytochemical markers CD31 and CD34, the endothelium of the papillary dermal vessels may present focal positivity for D2-40 and GLUT-1.[40-43]

Question 2
In patients with a clinic suggestive of capillary malformation, is the ultrasound color Doppler the most suitable first level examination to evaluate the morphological characteristics of the malformation?

Ultrasonography

The diagnostic protocol provides for the ultrasonography of the lower limbs as a first level study in the differential diagnosis with complex capillary-venous-lymphatic or capillary-arterio-venous vascular malformations, while second level exam is magnetic resonance (MRI).[44]

With routinely used probes, simple CMs are often not visible or appear as s focal thickening of the skin and subcutaneous tissue, compared to the contralateral area. Using high-frequency (20 MHz) ultrasound probes, it is possible to visualize the CMs as superficial hypoechoic areas extending from a depth of 0.2 mm to 3.7 mm, with an average depth of 1.0 mm. The Doppler ultrasound can show a slight increase in the density of dermal vascular signal when compared with the healthy contralateral dermis, reflecting the progressive dilation of ectatic capillaries.[45, 46] However, even with these tools, about 18% of CMs are not identified; moreover, the ultrasonography does not allow to visualize the superficial vessels and the characteristics of the most superficial portion of the CM. Therefore, it has been proposed the use of optical computed tomography (OCT), which is equivalent to ultrasound but with a resolution on a micrometer scale 10-100 times higher than ultrasound, MRI or computed axial tomography (CT), thus being similar to conventional histology. Additionally, OCT can be used to visualize moving particles using the Doppler effect and then for imaging.[47]

INTERPRETATION OF THE DATA

From the articles extracted from the literature on the subject (period from 2015 to 2020), three narrative reviews and an original article were selected.[44-47]

All the studies agree that the diagnosis of CM is mainly clinical, but in specific circumstances the Doppler ultrasound allows for the evaluation of any associated hemodynamic abnormalities and the use of high-frequency ultrasound probes represents an additional element of diagnosis.

The quality of the evidence, assessed through the various checklists, was overall good.

Recommendations
In the localizations of the lower limbs, the venous ultrasonography is essential for the evaluation of any hemodynamic abnormalities associated with capillary malformation in the context of screening for complex vascular polymalformative syndromes.
Recommendation of good clinical practice, based on the experience of the panel: GPP grade

Magnetic resonance imaging (MRI)

On MRI, CM may present itself as a subtle signal anomaly within the subcutaneous fat in the context of thickened skin.[46]
MRI with and without contrast medium can be useful for the study of associated anomalies in mixed or complex forms.[44] Furthermore, it is indispensable in the evaluation of central nervous system involvement.[46]

Other investigations

In the suspicion of complex or systemic syndromes, the protocol must be integrated with targeted instrumental investigations: MRI is the first-choice examination in the recognition of complex low-flow or high-flow malformation syndromes, and the relationship with surrounding tissues. CT is reserved for those cases where MRI is contraindicated or to highlight the presence of phleboliths, calcifications and bone involvement.[46]

A periodic check-up during the developmental age through orthopedic examination and comparative radiography of the lower limbs is indicated in the assessment of dysmetria if the CM is localized in the lower limb and it is associated with its overgrowth (see chapter on complex vascular malformations).

Furthermore, for those forms involving the cephalic extremity and in case of thickening of the CM, an evaluation by a multidisciplinary team is indicated.

Differential diagnosis

CMs can rarely mimic infantile hemangioma during the prodromal phase. Infantile segmental hemangioma of the face in the early phase preceding rapid growth can present in the form of a telangiectatic or a rosy red patch. Dermoscopy is a useful diagnostic aid.[48]

In the differential diagnosis, the arteriovenous malformation (AVM) in the initial quiescent phase (AVM in stage 1) must also be considered.

The diffuse reticular form must be differentiated from congenital cutis marmorata telangiectatica which is distinguished by the absence of telangiectasias and depressed and atrophic areas.

Treatment

Question 1
In patients with pure and untreated capillary vascular malformation, is the pulse-dye laser indicated as the first choice treatment compared to other types of vascular lasers?

Question 2
In patients suffering from capillary vascular malformation, should the pulse-dye laser treatment be started in childhood or is it advisable to carry it out in adulthood?

Question 3
In patients with pure capillary vascular malformation undergoing treatment with PDL, is the combination of topical drugs more effective than the pulse dye laser treatment alone?

Laser therapy

Pulsed dye laser (PDL) remains the treatment of choice in CMs.[49, 50] It works by selective photothermolysis of hemoglobin with microagglutination of intracapillary red blood cells which causes obliteration of the vessels without producing scarring. The selective target of this process are the dilated capillaries and the post-capillary venules of the reticular and papillary dermis located at an average depth of 1.2-1.5 mm and with a diameter between 10 and 500 micrometers.[51, 52] The latest generation PDLs deliver pulses at a wavelength of 595-nm; this wavelength, together with longer pulse durations, greater diameter of the spots (up to 15 mm) and the use of skin cooling devices that reduce thermal damage and painful sensation associated with the delivered pulse, allow overall use of higher energy levels than old generation PDLs.

Complete disappearance of CM following PDL treatment, resulting from complete photocoagulation of the target vessels, occurs in only 10% of treated patients;[53, 54] in most cases (about 70%) the therapeutic outcome results in a variable reduction of the CM chromatic intensity. In CMs that only partially respond to treatment, the level of clearing achieved may not be stable and lasting over time. The progressive ectasia of malformed capillaries due to reduced innervation, post-treatment neovascularization in the more superficial capillaries and neoangiogenesis starting from capillary structures of the deeper component that are not reached by the action of the PDL, mean that the results may not be maintained over time.[55]

The decision to undertake laser treatment depends on location and characteristics of the CM. Natural evolution of CM over time when left untreated, risks, benefits and limitations of treatment should be envisaged and discussed with the patient and families.[56, 57]

In particular, regarding CMs of the face, they can represent a stigmata source of stress and can determine low self-esteem.[58, 59] Although there are no prospective studies confirming that early PDL use reduces the natural progression of CM in terms of color, hypertrophy, and lumpiness,[60] clinical experience suggests that early treatment in the first years of life should be recommended given the greater efficacy on clearing the CM and given the consequent psycho-social benefits that follow.[61-64]

Depending on the anatomical site, the response to the laser is different: on the face, the centro-facial portions respond less effectively than the lateral portions.[65] The limbs, especially in the more distal and sloping parts, have a poor response to PDL.[66] The reasons depend on the fact that the skin areas with less response are characterized by greater dermis thickness, reduced innervation, greater capillaries' density and an excessively small or large vessel caliber.[67-70] which reduce the efficacy of photothermolysis because it is less selective. About 20% of CMs treated with PDL shows an ineffective and unsatisfactory response to PDL;[71] in this subgroup of patients, other types of lasers can be used secondarily in an attempt to improve the effectiveness of the treatment, but with a lower safety profile.[72, 73] Among the most used vascular lasers in recent years, dual wavelengths (DWL), have been shown to have an efficacy comparable to PDL in flat CMs, but has a worse safety profile being burdened by a higher percentage of side effects.[74] Its indication therefore finds space in the treatment of capillary malformations resistant to PDL and/or in hypertrophic forms. This sequential method involves the rapid delivery of a double PDL-Nd:YAG pulse. Those two pulses with different wavelengths (595 nm and

1064 nm respectively) are emitted at a distance of a fraction of a second and allow the preliminary transformation of oxyhemoglobin into methemoglobin and a subsequent penetration of the Nd:YAG radiation up to a depth of 7-8 mm.

In recent years, to improve the *outcome* of laser treatment, the complementary use of topical drugs with anti-angiogenic action has been used experimentally in an attempt to stabilize the lightening achieved through laser treatment over time. The literature on the subject includes the use of various active ingredients such as timolol,[75] imiquimod, rapamycin[76, 77] and axitinib. At the moment these topical drugs have still uncertain efficacy and are being evaluated in various clinical trials.[78]

INTERPRETATION OF THE DATA (QUESTION 1)

A meta-analysis, a randomized controlled study, three narrative reviews were selected from the 95 articles extracted from the literature on the subject (period from 2015 to 2020).[49, 50, 52, 73, 74]

All the studies, and in particular the meta-analysis of the literature, still agree that PDL 595-nm is still the first choice treatment in non-hypertrophic capillary vascular malformations that have not been subjected to previous treatments. While not proving to be the optimal treatment and presenting intrinsic limitations to the method, PDL still demonstrates the best efficacy and safety profile compared other lasers; therefore, in this type of CM there are no substantial advantages in using laser techniques other than PDL 595-nm. According to the only high quality randomized controlled trial comparing PDL with other vascular lasers in the treatment of CM, the DWL (Dual Wavelength Laser) shows an efficacy comparable to PDL, but burdened by greater side effects and is therefore considered second-rate treatment.

The quality of the evidence, assessed through the various checklists, was overall good. The main limitation to the scientific evidence on this topic is the lack of objective *outcome* measures in most studies, in the face of the widespread use of IGA scales on serial photographs, subject to dependent operator bias; outcome measures, in terms of clearing of CM, are overall not optimal in the literature, but satisfactory; the conclusions of all the studies, however, are consistent with each other and with the evidence of the literature prior to 2015.

INTERPRETATION OF THE DATA (QUESTION 2)

From the 95 articles extracted from the literature on the subject in the period from 2015 to 2020, four cohort studies and three narrative reviews were selected.[49, 52, 56, 62-64, 73]

The recommendation for PDL treatment in childhood is suggested in most of the works on the subject (all retrospective and prospective cohort studies and narrative reviews) because it allows to obtain greater efficacy of the laser treatment in relation to the morphological characteristics of the child's skin and of CM in this age group, as well as for the psychosocial advantage in terms of quality of life that early treatment entails. Although there are no prospective studies that clearly demonstrate that early treatment controls the pejorative evolution of CM and therefore this evidence is technically modest, the clinical importance of the other two aspects is such as to make a strong recommendation anyway. The quality of the evidence, assessed through the various check-lists, was overall fair. Not all studies reviewed were found to be relevant to the target population and many were discarded (adults only); many studies used only the pediatric population, avoiding a comparison with the adult response. The absence of a standardized and objective method that is easy to use in clinical practice to measure the outcome of laser treatment prevents the results of various clinical trials from being effectively compared, reducing the quality of scientific evidence and having a negative impact on clinical practice. An effort by the scientific community to identify an objective and unambiguous outcome measure would be desirable.

In the *outcome* measures, as already stated to respond to KQ1, *Investigator Global Assessment* (IGA) scales are often used on serial photographs subject to operator dependent *bias*; the *outcomes* of the results are not totally satisfactory and uniform; the conclusions are consistent with each other and with the literature prior to 2015.

In conclusion, the analysis of the literature suggests that early treatment is more effective and advantageous and therefore indicated. The clinical importance of the topic is very relevant to clinical practice and therefore, in the opinion of the panel, it determines a strong recommendation in favor.

INTERPRETATION OF THE DATA (QUESTION 3)

From the 95 articles extracted from the literature on the subject (period from 2015 to 2020), one narrative review, one randomized controlled trials, two case-series were selected.[75-77, 79]

PDL represents the gold standard in the treatment of CM, but has partial efficacy. Its use results in the majority of cases in incomplete clearance of CM despite numer-

ous treatment sessions. CMs, after an initial clearing, often tend to revascularize, as reported by many authors, after PDL treatment, as a consequence of the neoangiogenesis that occurs in the tissue remodeling phase. This accounts for the attempt to find alternative or complementary methods to improve laser results. The use of topical antiangiogenic therapy appears promising in this regard. From the evidence in the literature, imiquimod and rapamycin have shown some efficacy, but are currently still under evaluation. It is not possible to make a recommendation on the clinical effectiveness of their use. The quality of the evidence, assessed through the *check-list* for the analyzed literature, was found to be insufficient. The studies examined are designed on a small population and the conclusions are conflicting. The evidence is weak and too scarce in number to draw conclusions on the subject and make a recommendation on their use.

Considering the intrinsic limitations of the PDL method in the treatment of CM, certainly the identification of a topical treatment that can improve the effectiveness of laser treatment is a central topic on which research should make greater efforts; further prospective studies on antiangiogenic drugs on larger patient cohorts would help to draw more solid conclusions on the subject. The *pathways* involved in the maintenance of the lesion and in the remodeling of the endothelial tissue of CM need to be further investigated. More knowledge in this sense would translate in the identification of more effective and selective treatments.

RECOMMENDATION FOR RESEARCH AND FOR LIMITED USE IN CLINICAL TRIALS

Recommendations

Question 1: In patients with untreated pure capillary malformations, the Pulse-Dye Laser is indicated as the first choice treatment over other types of vascular lasers.
Strong recommendation in favor, level of evidence 1 ++

Question 2: In patients with capillary malformations, Pulse-Dye Laser treatment at an early age is indicated especially in the case of facial localizations.
Strong recommendation in favor, level of evidence 2+

Question 3: In patients with CMs treated with Pulse-Dye Laser, the combination of antiangiogenic drugs for topical use has given conflicting results. Further studies are needed to determine whether their use has any benefits over Pulse dye-laser treatment alone.
Recommendation for research and for limited use in clinical trials

Surgery

Surgery should be considered in selected cases: for the correction of hypertrophy of the facial bones associated with capillary malformations, for the removal of adult hypertrophic capillary malformations in the presence of polypoid vegetations, and to radically remove hypertrophic angiokeratomas.

The surgical technique utilizes *skin expanders* or rotational flaps for reconstructive purposes. Recently, free perforating flaps have been used for the reconstruction of the neck and face based on the thoraco-dorsal artery.[79-84]

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Guidelines for venous malformations

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Introduction

Definition

Venous malformations (VM) are congenital anomalies of the central or peripheral venous system caused by evolutionary errors in different phases of embryogenesis.

Histologically they are characterized by large vascular venous spaces. The walls can be thin or thick and fibrous, always covered by a flat monostratified endothelium, without atypias and mitotic activity. VM are more frequently localized in soft tissues and in the skin where the vessels appear wide and often delimited by a muscular wall, sometimes rich in elastic fibers, but always without an internal elastic lamina. In those VMs located in the central nervous system the wall can be thin or thick but still fibrous, while those in intraosseous areas have a thin wall with rare smooth muscle fibers. Endothelium is immunoreactive for endothelial markers CD31 and CD34, and negative for WT-1 and GLUT-1.[1-4]

Classification

The ISSVA 2018 classification (Table I) distinguishes common VM from rare forms that require multidisciplinary supervision and treatment with neurologists, neurosurgeons, orthopedists, dermatologists and radiologists.

The Hamburg Classification is very useful in the classification of common VM, which are divided into two radically different groups in terms of embryogenetic, anatomo-functional and clinical characteristics: malformations of the main veins (truncular forms) and malformations consisting of localized dysplastic veins in the tissues, at variable distance from the main venous axes (extratruncular forms).[4-8]

Table I.—*ISSVA Classification for Venous Malformations (VM) 2018.*

• Common VM
• Familial VM cutaneo-mucosal (VMCM)
• Blue rubber bleb nevus (Bean) syndrome VM
• Glomuvenous malformation (GVM)
• Cerebral cavernous malformation (CCM)
• Familial intraosseous vascular malformation (VMOS)
• Verrucous venous malformation (formerly verrucous hemangioma)
• Others

Truncular forms

They are observed more rarely. They consist of anatomo-functional alterations of the main venous axes and are caused by evolutionary anomalies during the most advanced stages of vascular embryogenesis.

They have a low proliferative potential; therefore the risk of post-treatment recurrence is limited. They induce significant hemodynamic effects on the district circulation, with venous stasis secondary to obstruction and/or reflux.

Truncular venous malformations are very variable: valvular anomalies (avalvulia or dysplasia), obstructive lesions (atresia, aplasia, hypoplasia, intraluminal membranous septa), dilated lesions (venous aneurysms), persistence of avalvulated embryonic veins (marginal vein, ischiatic vein).

Extratruncular forms

They represent the most frequent variety of VM. They can be circumscribed or they can extensively infiltrate the tissues. These are dysplastic veins resulting from an error that occurs in early stages of embryogenetic development of the vascular bed. They consist of undifferentiated vessels of mesenchymal origin with a high proliferative potential and are therefore characterized by a worsening evolution and a high rate of post-treatment relapses. They often produce compressive or infiltrative effects on the surrounding anatomical structures.

Recommendations

The identification of the embryological subtype (truncular or extratruncular) of a VM is important to establish therapeutic strategy.

Recommendation of good clinical practice, based on the experience of the panel

Epidemiology

VM are the most frequent congenital vascular malformations, representing about two-thirds of the total. Their incidence in general population is approximately between 0.8% and 1%.[2, 9]

Etiology

Most VM are sporadic. However, inherited forms with autosomal dominant inheritance have been reported.

The TIE2/TEK endothelial receptor for angiopoietin, whose gene is located on chromosome 9, has been identified as the cause of familiar mucocutaneous forms of VM. A variant of hereditary VM, called glomo-venous, is linked to abnormalities of the glomulin gene, located on the short arm of chromosome 1.

Some VM are accompanied by perivascular proliferation of cells normally present in the vascular glomas, similar to smooth muscle cells, and are referred to as glomovenous malformations or glomangiomas.[1, 2]

In Klippel-Trenaunay-Weber Syndrome, one of the most frequent complex VM, the molecular basis is not completely known, however in many cases a somatic mutation of the PIK3CA gene has been identified in the precursor cells from which the blood or lymphatic vessels of the affected area will develop. Since this alteration does not involve germ cells, the disease cannot be transmitted to offspring. However, some families with multiple affected members have been described; it is therefore likely that the molecular bases are heterogeneous.[10-12]

Natural history

In most cases, VM are evident from birth even if they sometimes manifest late. They do not undergo any spontaneous regression but persist throughout life and tend to progressively grow. The size increase of the lesions is usually slow and proportional to somatic development. An exacerbation can be observed during puberty or pregnancy due to estrogen-dependent hormonal changes. [13-15]

Clinical aspects

VM are mainly isolated lesions, but they can also be multifocal. The size and extent are extremely variable, as well as the type and severity of the anatomical-functional alterations.

They can be observed in any anatomical localization, preferring the limbs, the craniofacial, the pelvic-pudendal and thoraco-abdominal regions. Superficial, cutaneous, and mucous localizations are prevalent, but deep, intramuscular, intraosseous or visceral localizations are also observed.

VM can be associated with other congenital vascular malformations: capillary ("vascular macula") and lymphatic malformations.

Both truncular and extratruncular forms can cause severe clinical pictures and serious complications. [16-21]

Truncular VM produce hemodynamic changes and can determine chronic venous insufficiency (venous dysplasias, edema and stasis dermatitis, skin ulcerations).

In some cases, especially in limbs' localizations, it is possible to observe pictures of angio-osteo-hypertrophy or regional angio-osteo-hypotrophy, caused by anomalies of bone vascularization that alter skeletal development. These lesions define the so-called "vascular bone syndrome" and typically manifest themselves with a discrepancy of the extremities. Klippel-Trenaunay-Weber Syndrome is a significant example of this.

In the truncular forms there is a high incidence of deep vein thrombosis and pulmonary embolism.

Superficially localized extratruncular VM are clinically very evident and typically present as bluish or purplish swelling, with a soft-elastic consistency, not pulsating, expandable and collapsible under compression. The deep forms are not very evident, and they are very difficult to diagnose with a simple physical examination: the most frequent clinical signs in these cases are the swelling that increases in volume with the postural change, especially in craniofacial malformations, and local pain. Infiltrating forms can cause signs and symptoms of compression of the surrounding anatomical structures (nerve, muscle-tendon, osteo-articular, visceral). In extratruncular VM, coagulopathy is often present (40% of cases), caused by venous stasis and by the activation of the coagulation cascade with a tendency to form intraluminal thrombi in dysplastic vessels. This pathological picture is called "localized intravascular coagulation" (LIC) and is characterized by elevated levels of D-dimer and PDF associated with normal platelet counts and sometimes with reduced levels of fibrinogen. Calcification of intra-vascular thrombi can lead to the formation of hard nodules known as "phleboliths."

Thrombotic complications are observed more frequently in very extensive and infiltrating forms.

Question 1
Is a complete coagulation screening including fibrinogen assay and D-dimer required to assess the presence of a chronic coagulopathy in venous malformations?

The following recommendation was imported from previous SISAV guidelines of 2015. Recent literature review has revealed no evidence of changes in previous recommendations.

Recommendations
It is advisable to always search for the coexistence of other vascular malformations (capillary, lymphatic, arteriovenous) for a complete diagnostic framework.
Recommendation of good clinical practice, based on the experience of the panel

In VM, a complete coagulation screening including the D-dimer assay is useful to assess thrombotic risk and the presence of LIC.
Recommendation of good clinical practice, based on the experience of the panel

Diagnosis

Question 2
In patients with a clinic suggesting a common VM, is the Echo-Color-Doppler the most suitable first level examination to evaluate the morphological and hemodynamic characteristics of the malformation?

Echocolordoppler

Echo-color-Doppler provides information on morphological and hemodynamic characteristics of the malformation. [22-26]

In "B-mode" the morphological evaluation is performed: VM typically present as hypo- or hyper-echogenic vascular lacunae compressible with probe-pressure, localized in the subcutaneous or deep soft tissues.

In "duplex" mode, the hemodynamic study shows a characteristic low-speed venous flow, evoked by compressive maneuvers, within the dysplastic lacunae, and the hemodynamic characteristics of the malformation and the entire venous system can be studied.

It is desirable that the Echo-color-Doppler examination is performed by an experienced operator to obtain reliable diagnostic information.

INTERPRETATION OF THE DATA

To answer question 2, a consensus statement and two narrative reviews of the literature were identified[22-24] which considered ultrasound imaging as a first level method in the diagnostic process.

The conclusions of the analyzed studies are consistent with each other. Experts agree in indicating the Echo-Color-Doppler as a first level instrumental examination for VM, as it allows an initial, rapid and non-invasive evaluation of the main characteristics of the VM: extension, hemodynamics and morphology. The investigation is completely risk-free. The impact on the patient is minimal, as it is a non-invasive assessment. The feasibility is good in the entire national context but, being an operator-dependent examination, it should be performed by experienced personnel in the field.

Studies are relevant to the target population. Bias: the sample examined in the various studies is always small, given the rarity of the disease. Furthermore, there are no studies that statistically compare the echocolordoppler with other first-level diagnostic methods.

Recommendations
In patients with a clinic suggesting a common venous malformation, it is indicated to perform the Echo-Color-Doppler as a first level examination, to evaluate the morphological and hemodynamic characteristics of the malformation.
Strong recommendation in favor, level of evidence 4

Question 3
In patients with Doppler ultrasound suggestive of common VM, what are the second level instrumental examinations most suitable to perform an adequate preoperative evaluation of the malformation?

Magnetic resonance imaging

Magnetic resonance imaging (MRI) allows you to confirm the type of VM, to assess the extent, anatomical relationships and infiltration of tissues in the extratruncular forms, to highlight the venous drainage circles. [27-33]
Dysplastic venous vessels typically present as iso-hypointense lacunar areas in T1-weighted sequences and hyperintense in T2-weighted sequences and after adipose signal suppression. After intravenous injection of paramagnetic contrast medium, a characteristic enhancement is observed with possible presence of fluid-fluid levels in ectasias with flow stagnation. Intraluminal calcifications appear as hypointense focal areas.

The contrast medium method also provides hemodynamic information on the flow rate within the malformation.

INTERPRETATION OF THE DATA

To answer question 3, a consensus statement and two narrative reviews were analyzed.[22-24]

The studies agree on the execution of MRI with contrast medium as a second level instrumental examination, after Echo-Color-Doppler. This investigation allows to complete the diagnostic evaluation of the VM in terms of extension, involvement of surrounding tissues and internal organs, vascularization. The examination does not involve significant risks and has an acceptable impact on patients, considering that it is necessary to plan the surgical intervention. It is easily implemented throughout the country, but the interpretation of the images should be performed by radiologists with expertise in the field.

Studies are highly relevant to the target population. The conclusions are consistent. Bias: there are no recent stud-

ies that aim to demonstrate the diagnostic superiority of a method in a statistically significant manner.

Recommendations
In patients with color Doppler suggestive of VM, it is indicated to perform MRI with contrast administration, as a second level examination, for a complete preoperative evaluation.
Strong recommendation in favor, level of evidence 4

Computed tomography

Computed tomography (CT) is less valid than MRI in assessing extratruncular VM. However, if performed with contrast medium, it can be useful in the study of truncular VM, both central and peripheral, highlighting stenosis, aplasia, venous aneurysms, embryonic venous circulation.[34-37]

The CT examination is of great use in craniofacial VM for the study of the relationship with the cranial theca and the search for any extra-intra-cranial venous communication.

INTERPRETATION OF THE DATA

There are no adequate studies to evaluate the scientific evidence of the role of CT in the diagnosis of VM.

Recommendations
CT with contrast medium may be useful in some cases: in extratruncular VM to study skeletal involvement, in truncular VM for preoperative anatomical evaluation, in craniofacial VM for the search for extra-intra-cranial communication.
Recommendation of good clinical practice, based on the experience of the panel

Phlebography

Phlebography is an invasive examination whose role in the preoperative diagnosis of VM has been significantly reduced because the data provided by echocolordoppler and MRI, possibly integrated by CT, are usually sufficient to obtain a complete picture.

Ascending phlebography allows to evaluate the patency and hemodynamics of the deep venous circulation. Descending phlebography is useful in the study of congenital deep venous incontinence due to valve malfunction, linked to cusp anomaly, valvular asymmetry, hypoplasia or aplasia of the same.[38] Phlebography by direct puncture allows to evaluate the course of the embryonic venous trunks or the discharge veins of extratruncular VM and must be performed in the intraoperative diagnostic phase before surgical treatment or scleroembolization.[5-7]

INTERPRETATION OF THE DATA

There are no adequate studies to evaluate the scientific evidence of the role of venography in preoperative diagnostics of VM.

Recommendations
Phlebography should be reserved to preoperative study of complex VM or for intra-operative monitoring of sclero-embolization treatments. Arteriography is of no use and should therefore be avoided.
Recommendation of good clinical practice, based on the experience of the panel

Question 4
In patients diagnosed with MRI of pharyngo-laryngeal and laterocervical VM, is it appropriate to perform a preoperative laryngoscopy to assess the risks associated with intubation and post-scleroembolization edema?

Laryngoscopy

In cases of cervical VM with pharyngo-laryngeal involvement and involvement of the upper airways, diagnosed by MRI, a preoperative laryngoscopy allows you to assess the risks of intubation and post-scleroembolization edema.[39-41]

INTERPRETATION OF THE DATA

To answer Question 4, a consensus statement and a systematic review[22, 39] on the treatment of cephalic VM were analyzed.

Studies agree that laryngoscopy is advantageous as it allows an adequate assessment of the operative risks related to intubation and post-scleroembolization edema and allows to establish the possible indication for a preventive tracheostomy. The risks of the examination are limited to transient laryngeal disorders.

The feasibility is good throughout the national territory. The impact on the patient is high, on an emotional level, in the event that the laryngoscopy determines the need of a tracheostomy.

The quality of the evidence, assessed through the checklist for systematic reviews, was found to be acceptable. The analysis of the studies highlights a clear relevance for the target population, consistent conclusions and the absence of potential bias.

Recommendations
In patients with pharyngolaryngeal and laterocervical VM, it is advisable to perform preoperative laryngoscopy to assess the risks associated with intubation and post-scleroembolization edema.
Strong recommendation in favor, level of evidence 1+

Treatment

Question 5
Are conservative treatments appropriate, in combination or replacement of invasive treatment, to improve the quality of life of patients diagnosed with common VM?

Elastocompression

Elastocompressive therapy with elastic bandages or braces can be useful especially in VM of the lower limbs, particularly in truncal forms with chronic venous insufficiency to improve symptoms related to peripheral venous hypertension.[42]

Physical therapy

Physiotherapic treatments can help in selected cases.[43] Manual lymphatic drainage is indicated in combined hemolymphatic malformations. The use of orthopedic braces is useful for improving functionality and quality of life in forms associated with skeletal abnormalities (for example, corrective insoles in venous malformations with lower limb discrepancies).

Pharmacological therapy

Some studies suggest the usefulness of sirolimus in selected cases of gravity[44] but the scientific evidence on this therapy is still insufficient.

Treatment with low molecular weight heparin (LMWH) is indicated in VM with clinical signs of LIC, especially in presence of hypo-fibrinogenemia.

INTERPRETATION OF THE DATA

To answer Question 5, two systematic reviews were analyzed, a narrative review of the literature and a retrospective cohort study.[18, 23, 42, 45]

All studies indicate the usefulness of conservative treatments such as elastic compression and drug therapy with LMWH in patients with complicated and localized common venous malformations. These treatments make it possible to reduce the incidence of complications such as thrombosis or ulcerative lesions without inducing adverse events. These are acceptable therapies for patients, even if they are necessarily chronic, as they improve the quality of life. The feasibility is good, as they are easily accessible and low-cost therapies.

The quality of the evidence, assessed using the Checklist for systematic review and cohort studies, was found to be good. Studies are relevant to the target population; the conclusions are consistent. Bias: heterogeneity of the population under examination and of the pathology; small sample.

Recommendations
In patients with VM, it is indicated to combine appropriate conservative treatments, such as medical therapy and elastic compression, especially in the presence of complications.
Strong recommendation in favor, level of evidence 1+

Question 6
In VM with disabling symptoms, haemodynamic changes and severe complications, is invasive treatment indicated to improve the quality of life and haemodynamics of the malformation?

Invasive treatment

Invasive treatment of a VM is commonly performed in the presence of severe symptoms or complications: hemorrhages, chronic venous insufficiency, disabling pain, functional deficits, aesthetic deformities, osteo-angio-dystrophic syndrome, compromise of vital organs, thromboembolism.

INTERPRETATION OF THE DATA

To answer Question 6, a systematic review and meta-analysis, a retrospective cohort study and a narrative review were analyzed.[23, 45, 46]

All studies indicate the need for invasive treatment in case of disabling clinic for the patient, hemodynamic alterations or severe complications related to the malformation.

These treatments allow to significantly improve the quality of life of patients, despite being burdened by the risk of possible complications such as skin necrosis, pulmonary thrombo-embolism, neurotoxicity, non-eradication of the malformation, unsightly skin scars.

These are acceptable therapies for patients, considering the significant aesthetic and functional benefits. In terms of feasibility, these interventions are highly specialized and can therefore only be implemented in centers with proven experience in the field of vascular malformations.

The quality of the evidence was assessed using the Checklist for systematic review and cohort study, being good for the former and acceptable for the latter. Studies are relevant to the target population, the conclusions are consistent. Bias: heterogeneity of the sample and absence of a standardized assessment of the quality-of-life improvement.

Recommendations
Invasive treatment is indicated in all VM with disabling symptoms, haemodynamic alterations and severe complications, to improve the patient's quality of life and the haemodynamics of the malformation itself.
Strong recommendation in favor, level of evidence 1 ++

Question 7
In VM, what is the effectiveness of scleroembolization as the main treatment, compared to surgery?

Scleroembolization

Scleroembolization is the most common method in the treatment of VM, as it allows good results combined with low invasiveness.

It is usually practiced either as an alternative or in combination with surgery.[47-64]

It consists of the percutaneous injection of various sclerosing agents in order to obtain the occlusion of dysplastic vessels and the destruction of their endothelium.

It can be performed on ultrasound or fluoroscopic guidance. Ultrasound is useful in the percutaneous puncture phase to locate the malformation and to check the position of the needle. Percutaneous fluoroscopy allows for intraoperative diagnosis of the VM and the discharge routes in the veins of the deep circulation, in particular in craniofacial and pelvic VM. It is also essential to monitor the spread of the sclerosing agent, suitably mixed with a contrast medium, within the malformation.

INTERPRETATION OF THE DATA

To answer question 7, four systematic reviews of the literature were analyzed[39, 46, 64, 66] which indicate the efficacy of scleroembolization with different agents, without clearly defining the superiority of one of these, both as a pretreatment and as an elective treatment.

All studies show that scleroembolization has the advantage of reducing the size of venous malformations with less bleeding and less aesthetic impact than surgery, inducing a significant improvement in clinical symptoms and hemodynamics. These benefits outweigh the risks of local and systemic complications including skin necrosis, pulmonary thromboembolism and neurotoxicity.

The impact on patients is acceptable, even considering that repeated interventions are often necessary over time and that transient local disturbances (edema and pain, treatable with cortisone and analgesics) occur in the immediate post-operative phase. The feasibility of the intervention is limited to centers specialized in the treatment of vascular malformations.

The quality of the evidence, assessed through the Checklist for systematic review, was found to be of a good level. The conclusions of the studies are consistent, without conflict. The relevance for the target population is absolute and no bias are evident.

Recommendations
In the invasive treatment of VM, scleroembolization is indicated both as a pre-treatment and as an elective treatment.
Strong recommendation in favor, level of evidence 1 ++

Question 8
In scleroembolization of VM, what ethanol dosage should be used to minimize the risks?

Sclerosant agents

Ethanol is the most widely used sclerosing agent in the scleroembolization of VM, being commonly considered the most powerful and effective. In clinical experience it allows for better results than other sclerosing agents but, if not properly used by expert personnel, it is burdened by a high morbidity rate. Complications can be local and systemic: skin ulcerations, neuropathies and thromboembolism. The risk is greater in VM localized in the mucocutaneous area, near peripheral nerves or in acral regions. Since the injection of ethanol is very painful, a loco-regional or general anesthesia is required.

Polidocanol (1-3%), sodio-tetradecyl-sulfate (0.2-3%) and bleomycin are alternative sclerosing agents in the treatment of VM, mainly used for their low morbidity. They are mainly administered in the form of foam. They are especially indicated in VM with superficial, cutaneous or mucosal localization. These sclerosing agents allow satisfactory clinical results to be obtained by reducing the risks of cutaneous or neurological side effects. The main limitation is the high incidence of distant relapses, compared to ethanol. An elevated risk of embolic-based neurological complications should also be reported in patients with patency of the foramen ovale or other right-to-left shunts.[68-80]

Recently, the use of Glubran-2 has been introduced in pediatric VM, a biodegradable synthetic glue based on cyanoacrylate, modified by the addition of a monomer synthesized by the manufacturer GEM. This procedure is used pre-surgically in patients with localized malformations, to reduce the massive bleeding related to the surgical procedure.[82]

INTERPRETATION OF THE DATA

To answer question 8, two systematic reviews of the literature were analyzed in a consensus document.[5, 46, 64]

These studies agree on the use of a maximum dose of 1-2 mL/kg of ethanol to minimize the risks related to the treatment. This dosage allows to treat even larger malfor-

mations, obtaining satisfactory results and significantly reducing the risks of adverse events. The recommended dose reduces the impact on patients in terms of postoperative edema and complications. Dosage evaluation is the prerogative of centers specialized in the treatment of vascular malformations.

The quality of the evidence, assessed using the Checklist for Systematic Reviews, was found to be good. The conclusions of the studies are consistent with each other. Relevance to the target population is recognized and no publication bias is detected.

Recommendations

In the scleroembolization of VM it is recommended not to exceed the dose of 1-2 ml / kg of ethanol, in order to minimize the risks of complications related to the treatment.
Strong recommendation in favor, level of evidence 1 ++

Question 9

In focal VM or with embryonic veins, is an ablative surgical treatment indicated?

Venous ablative surgery

Surgical excision is the most effective treatment of extratruncular VM in all cases in which it is possible to ensure radical removal of the lesion, both as an isolated procedure and in combination with scleroembolization.

The main indication is represented by focal and circumscribed VM, both in the superficial cutaneous-mucosal localizations and in the deep localizations involving a single muscular belly or in intra-articular forms, in particular of the knee.

However, surgical removal is burdened by high morbidity, especially in very extensive and infiltrating VM, in which a significant risk of bleeding, neurological lesions and relapses is described. In complex forms the risk of complications can be reduced, if possible, with a surgical approach in multiple sessions. [82-86]

Surgical removal is commonly recognized as the *gold standard* in the treatment of truncular VM with persistence of embryonic veins, such as the marginal vein. In these cases, the marginal vein is disconnected from the deep venous circulation, the anatomy of which often appears variable and therefore must be appropriately documented by an accurate diagnosis. Subsequently a plurisegmentary excision is performed through multiple skin micro-incisions along the course of the anomalous vein. Stripping is sometimes feasible, but is burdened by a discrete bleeding risk, which can be reduced by correctly mapping the collateral veins of the marginal vein.

Removal of embryonic veins should be performed as early as possible, even in childhood, to prevent the development of an osteo-angio-dystrophic syndrome. Exeresis of embryonic trunks is considered contraindicated in cases where atresia of the deep venous circulation coexists. [87-90]

INTERPRETATION OF THE DATA

To answer Question 9, a systematic review and a narrative review of the literature were analyzed.[18, 23]

The studies examined agree on the indication for surgery in focal VM, especially in the presence of thrombosis, and in VM with persistence of embryonic trunks such as the marginal vein. In focal lesions, surgery offers the advantage of radical and definitive removal. In case of embryonic veins, ablative surgery makes it possible to abolish reflux and venous hypertension, preventing the development of an osteo-angio-dystrophic syndrome. The need for a disconnection from the deep venous circulation is highlighted.

If the indication is appropriate, ablative surgery does not cause harm to the patient. In this sense, the fundamental importance of excluding any atresia of the deep venous axis in the preoperative phase is recognized. As these are highly specialized interventions, they can only be practiced in dedicated centers.

The quality of the evidence, assessed using the Checklist for systematic review, was found to be good. The studies are consistent in conclusions, relevant to the target population. Bias: the sample examined in the various studies is always small, given the rarity of the disease and the heterogeneity of the treatments.

Recommendations

In focal VM, especially if thrombosed, and in malformations with persistent embryonic veins, ablative surgery is particularly indicated. It is recommended to exclude any atresia of the deep venous circulation with instrumental examinations, which contraindicates ablative surgery of the embryonic trunks.
Strong recommendation in favor, level of evidence 1+

Reconstructive venous surgery

Reconstructive surgery is indicated in some forms of truncular VM.[5, 91, 92]

Surgical excision is the simplest and most effective method in the treatment of congenital intraluminal septa or venous membranes.

Total surgical resection followed by venous grafting/transposition or partial surgical resection followed by endorrhaphy are indicated in congenital aneurysms of deep

veins (such as the popliteal or superficial femoral) to prevent possible thromboembolic complications.

The correction of deep venous axial reflux can make use of different methods:

Internal valvuloplasty is possible in the presence of malfunctioning cusps while in the case of hypoplasia or aplasia, interventions such as valve grafting, femoral transposition or neovalve can be performed.

External valvuloplasty or venous banding interventions have not led to satisfactory results, while the implantation of valved prostheses is still in the experimental phase.[89, 90]

Percutaneous transluminal angioplasty, usually completed by the implantation of an endovascular stent, has proven effective in the treatment of congenital obstructions of the deep veins (at the iliac-femoral level).

INTERPRETATION OF THE DATA

There are no adequate studies to evaluate the scientific evidence of the role of venous reconstructive surgery in truncular VM.

Recommendations

Different methods of reconstructive surgery can be indicated in the anomalies of the venous trunks: resection of congenital septa, venous grafting or transposition, aneurysmorrhaphy, valvuloplasty, angioplasty and venous stenting.

Recommendation of good clinical practice, based on the experience of the panel

Laser surgery

Laser therapy can play a complementary role in the ablative treatment of VM. It can be performed with the use of different methods based on the location and extent of the VM.[92-95]

Different wavelengths can be used (diode laser with wavelength between 1310 and 1470 nm or Nd: YAG laser with 1064 nm wavelength). The following application methods are distinguished:

- transdermal or transmucosal in superficial forms (especially of the oral cavity);
- interstitial in the subcutaneous forms;
- endoscopic in visceral forms;
- endovascular in the treatment of truncular VM, especially for occlusion of embryonic veins such as the marginal vein.

The endovascular laser photocoagulation procedure is performed percutaneously by endoluminal insertion of a bare diode laser fiber. The maximum power used varies from 10 to 15 W according to the caliber of the cannulated vessel.

Cryotherapy and radiofrequency ablation have also recently been proposed for the treatment of selected cases.[96-98]

INTERPRETATION OF THE DATA

There are currently no adequate studies to evaluate the scientific evidence of the role of laser therapy in the treatment of VM.

Recommendations

Laser therapy can be an alternative to scleroembolization or surgery in selected cases of VM, by a transmucosal route in oral cavity localizations.

Recommendation of good clinical practice, based on the experience of the panel

Question 10

In patients with extensive craniofacial VM, is it advisable to perform reconstructive plastic surgery to ensure the best aesthetic-functional result?

Craniofacial plastic surgery

Surgery of vascular malformations of the craniofacial region has the maximum radicality as its first objective. However, there is also the need to look for a result that is as aesthetic as possible, preserving the symmetry of the face and obtaining minimal scars.

For this reason, reconstructive plastic surgery is widely used in cephalic VM, especially after very extensive demolitive operations.[99-102]

First of all, the surgical access is preferably performed from the oral cavity or it is chosen among the aesthetic surgery accesses, such as those for facelift or blepharoplasty are used.

The reconstructive phase is generally carried out by creating bundle-skin flaps that allows you to reshape the natural lines of the face. If necessary, the implantation of skin expanders is used in a phase of preparation for the definitive intervention.

INTERPRETATION OF THE DATA

To answer Question 10, two systematic reviews[22, 39] on the treatment of cephalic VM were analyzed.

The analyzed studies conclude that reconstructive surgery significantly improves the aesthetic-functional results in patients undergoing surgical resection of craniofacial VM with extensive tissue demolition. No significant risks are reported in the post-operative course. The impact on patients is favorable with a tangible improvement in the quality of life. The procedure is accessible in all competent centers.

The quality of the evidence was assessed through the checklist for systematic reviews, from which it was found to be acceptable for both papers. There is full consistency between the conclusions of the studies, which are objectively relevant to the target population. Bias: most studies do not focus on statistically significant assessment of quality-of-life improvement.

Recommendations

In extensive craniofacial VM, it is indicated to perform reconstructive surgery to ensure the best aesthetic-functional result.

Strong recommendation in favor, level of evidence 1+

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Guidelines for arterio-venous malformations

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Introduction

Definition

Arteriovenous malformations or AVMs are defined as anomalous communications between arterial and venous vessels, connected to each other directly or through a network of vessels called "nest". The cause is an evolutionary error in different stages of embryogenesis. Regardless of the presence of a "nest" or micro / macro fistulous tracts, AVMs can be classified as "high flow" malformations. This peculiarity may be responsible for secondary alterations on the arterial and/or venous district in the body segments involved, with local complications of ischemic or hemorrhagic type, district hemodynamic consequences and in extreme cases hemodynamic consequences involving the entire cardiovascular system. The acronym AVM is often improperly attributed to low flow malformations (VM) or also to vascular malformations in general: this use must be considered incorrect and a source of confusion.

Classification

AVMs can be distinguished in "truncular" forms (direct a-v communications) and "extratruncular" forms (characterized by indirect connections between small and medium caliber vessels with or without the presence of a "nest"). This terminology derives from the Hamburg classification, based on pathophysiological concepts.[1] The most recent ISSVA classification[2] is based on the same concepts and also distinguishes truncular and extratruncular forms, but it uses different terms: "major vessel anomalies" for the truncular forms and "simple forms" for the extratruncular ones.

The former (truncular forms) are rather rare and characterized by a direct and unique arteriovenous communication between large and medium caliber vessels. The second (extratruncular) represent the great majority of cases.

Truncular or extratruncular AVMs can be an integral part of some forms of genetically defined complex or syndromic vascular malformations (S. of Osler-Weber-Rendu, S. of Parkes-Weber, CLOVES, etc.).

There are two specific morphological/hemodynamic classifications of AVMs: Cho et al.'s classification and Yakes' classification.

TABLE I.—*Clinical staging according to Schobinger (1977).*[23]

Schobinger clinical staging
Stage I: Quiescence: no symptoms. Esthetic impact possible
Stage II: Expansion: stage I + functional impact (enlargement, pulsation, thrill)
Stage III: Destruction of tissues: Stage II + necrosis/ulcer/bleeding
Stage IV: Decompensation: Stage III + congestive cardiac failure

Cho *et al.*[3] distinguished the following types (Table I):

- type 1: arteriovenous connection with a maximum of three arteries entering in a single outflow vein;
- type 2: multiple small arterioles entering a single large draining vein;
- type 3a: multiple fine, non-dilated, arteriovenous shunts between arteries and veins;
- type 3b: multiple, arteriolovenous fistulas with dilated fistulous vessels between arteries and veins.

Subsequently, Yakes[4] integrated this morphological classification by adding the group of direct communications (type 1) and the group of retiform microfistulas (type 4):

- type 1: direct communications between arteries and veins;
- type 2: multiple arteriolar connection with veins through a "nidus";
- type 3a: multiple arteries entering a sole aneurysmal vein with a single outflow;
- type 3b: as 3a but with multiple venous outflow;
- type 4: area of microfistulous net diffusely infiltrating tissues.

The classification is useful, not only from an academic point of view, but also as a basis for subsequently orienting the diagnostic-therapeutic path. It is not always easy to determine the type of AVM based on the tests performed.

Epidemiology

To date, no environmental, geographical, ethnic or gender factors have been identified that could determine the prevalence of these malformations. The identification of the incidence of vascular malformations in general, and of arteriovenous forms in particular, is difficult due to confusing terminology and diagnostic classification, particularly in the frequent lack of differentiation between hemangiomas

and arteriovenous malformations. In a review of 238 studies including over 20 million births, the incidence of vascular malformations of all types was 1.08% on average, with a range across studies of 0.83 to 4.5%. [5] However, the study does not allow to establish the incidence of AVMs, which can be deduced from other analyzes. According to a study by Tasnadi (on 3573 3-year-old children) and by BB Lee (on a group of 1475 cases of peripheral vascular malformations), the incidence of AVM is 12%. [6,7] Other and more numerous data, however, refer to cerebrospinal AVMs, showing an AVM incidence of 18 per 100,000 people.[8]

Etiology

Advances in the field of genetics of simple and complex vascular anomalies have led to the identification of causative genes, inheritance patterns and disease mechanisms.

The advent of next-generation sequencing has made it possible to approach the routine genetic diagnosis of the various types of vascular malformations in a massive and parallel way.[9] Together with the identification of the two main pathways involved in etiopathogenesis (RAS/MAPK and PI3K/AKT/mTOR), this has led to the development and access of specific drug therapies for patients.[10]

Two types of clinical pictures are known for AVMs: syndromic and non-syndromic. The former include the different forms of hereditary hemorrhagic telangiectasia (HHT) and PTEN hamartoma-tumor syndrome (PHTS): two mendelian, autosomal dominant conditions caused by heterozygous germline mutations in associated genes (HHT: ACVRL1, ENG, GDF2, SMAD4-PHTS:PTEN). In both syndromes, high flow vascular malformations represent only part of the multiple phenotypic traits.[11] Non-syndromic pictures include isolated and sporadic forms of AVMs caused by somatic mosaic mutations in several genes (MAP2K1, BRAF, KRAS).[12, 13] This condition, defined as somatic mosaicism, implies the co-presence of two or more genotypically distinct cell lines that originate from the advent of post-zygotic mutations in the same individual.[14]

In particular for the MAP2K1 gene, the somatic mutations seem to be exclusively affecting the endothelial cells present in the vascular lesion.[12, 13, 15]

There is another genetic pathology known as capillary-malformation-arteriovenous malformation (CM-AVM) type I and II (the genes respectively involved are RASA1 and EPHB4) that causes the onset of AVMs in the context of other vascular anomalies. In CM-AVM type I, the disease mechanism would appear to be the presence of a heterozygous germline mutation in combination with a second mutational event.

Physiopathology

The high-pressure arterial system and the low-pressure venous system communicate with each other through the capillary system which has the function of maintaining a delicate balance between these two systems at different pressure. In case of anomalous direct communication between the arterial and venous systems, "skipping" the capillary system ("short circuit") due to an AVM, the balance mechanism of the capillary system itself between the two systems is lost. Downstream of the AVM, the arterial pressure is more or less reduced due to the diversion of a part of the blood towards the low resistance zone: the AVM itself.[17] If the hemodynamic effect of the AVM is modest, the pressure drop may also be not very evident; if instead the abnormal communication is significant, the pressure drop can cause peripheral ischemia.[18] On the other hand, in the venous system there is a phenomenon of hypertension due to the increased blood flow. In turn, venous hypertension has an overload effect on cardiac work, both arterial and venous. The body responds to these hemodynamic alterations with adaptational phenomena. In the first period, called compensation, there is an increase in cardiac output which has the purpose of maintaining an adequate arterial flow despite the lower peripheral resistance. In the phase of decompensation, there is degeneration of the arterial wall with tortuosity and aneurysmal dilatation, venous dilatation with valvular insufficiency and peripheral reflux, skin ulceration and hemorrhagic phenomena, generally from rupture of superficial hypertensive veins. In the late stages, heart dilation and decompensation appear.[19, 20] This last phenomenon, however, is less frequent than was once thought. The trend towards evolution, which varies from case to case, requires continuous clinical-instrumental monitoring and a highly flexible therapeutic strategy.

Natural history

Arteriovenous malformations are present from birth, but can remain silent for years without showing signs of themselves. About 80% is recognized in childhood.[21] The general trend is of progression with sudden worsening, which can be related to hormonal changes during puberty or during pregnancy, but also triggered by trauma. Spontaneous regression does not seem possible.[22]

Clinical aspects

From a clinical point of view, AVMs are classified according to Schobinger in four stages that consider the differ-

ent clinical impact and the consequent need for treatment (Table I).[23]

Typically, an AVM looks very different depending on the site and on the Schobinger stage.

In stage I, the AVM may not be evident or manifest only with a slightly exuberant area, sometimes as a cutaneous nevus or a slight redness, sometimes faintly pulsating, easily confused with a capillary malformation (PWS).[24] Symptoms may be absent or manifest only as a sensation of a hyperthermic and sometimes throbbing area. In stage II the mass can increase in volume (in deep localizations it is not always evident: there may be a slight increase in the volume of a limb) and presents itself as a hot, hyperemic mass, animated by abnormal pulsation and / or tremors, with possible evolution characterized by swelling and hypertrophy of the tissues involved, including bone segments. Hypertrophy can also manifest itself with elongation of one extremity resulting in a discrepancy between the two limbs. [25,26] In the case of an AVM located in the lower limb, a particular skin manifestation known as acroangiodermatitis (or pseudokaposis sarcoma) may show itself in the form of papules and/or discolored violaceous/purple lesions.[27] In stage III, areas of skin necrosis progressively appear, evolving towards ulceration. Bleeding from the ulcer can occur suddenly and can be copious. In stage IV, the AVM flow increases, thus increasing the flow to the heart and leading to heart failure.[28]

The malformation has a tendency to a progressive worsening in variable times.[29, 30] In a study of 446 patients, a progression of Schobinger's stage I was observed in 41.9% before adolescence, 80% before adulthood and 96.2% thereafter. Extensive lesions are more likely to evolve than limited ones. [31] The clinical evolution of AVMs is accelerated by traumatic or biological events (puberty, pregnancy) and also by the intake of estrogen-progestin.

Diagnosis

Clinical examination

The first framing of the patient takes place through a clinical examination, which must always precede the instrumental examinations. This approach provides useful data for an orientation towards diagnosis. Purplish or reddish discoloration of the skin may be observed. Local hyperthermia, dilated skin veins and a sensation of abnormal pulsation and shivering are other typical signs. However, these signs are not always evident. Dystrophic skin, ulcers with no tendency to heal, local pain and recurrent bleeding phenomena are signs of a worsening of the situation. The presence of dyspnea may indicate cardiac involvement which can be investigated by ECG and echocardiogram.

Recommendations

The careful clinical examination must highlight the signs of AVM and obtain a first impression on the Schobinger stage.

Recommendation of good clinical practice, based on the experience of the panel

Instrumental diagnosis

Instrumental and imaging diagnostics of AVMs include:

- continuous wave doppler (CW);
- Doppler ultrasonography (USD);
- MRI with contrast;
- CT scan with contrast;
- selective angiography.

Other diagnostic methods are considered optional and/or supplementary, which may be indicated in specific cases and in the opinion of the physician expert in the field:

- X-ray handwriting;
- total body scanning (WBB-PS);
- lung perfusion scanning (TLPS).

Doppler CW

CW Doppler, also in pocket version, allows the immediate recognition of the high turbulent flow characteristics of the AV vascular lesion with the relative accentuation of the diastolic component. It may be less effective in deeply localized forms.

Doppler ultrasonography

In the context of non-invasive diagnostics, more information can be obtained through Doppler ultrasonography (USD). It is a non-invasive procedure that allows a diagnosis of AVM based on the flow characteristics and a tissue identification. Echocolordoppler provides information on the morphological and hemodynamic characteristics of the malformation.

In the "B-mode" the morphological evaluation is performed: AVMs typically present as hypo or hyper-hypoechoic vascular lacunae, not always fully compressible at the probe pressure and localized in the subcutaneous or deep soft tissues.

In the "duplex" mode, the hemodynamic study is performed: a characteristic high-speed turbulent arteriovenous shunt flow is detected within the areas of the malformations. From an arterial point of view, there are the

typical flow rate increase and the resistance and Pulsatility Index decreases, while a pulsed flow can be detected within the efferent venous vessels.

The Doppler ultrasound can recognize, visualize and localize the presence of arteriovenous communications, including at the visceral, skeletal muscle and nerve tissue levels.[32-34]

The advantages of the Doppler ultrasound are the absence of radiation, the wide availability of devices, the possibility of use even at the patient's bed or in the operating room. Its limits are linked to a reduced precision in the deep tissues and to the lack of a 3D reconstruction technology. It is desirable that the Doppler ultrasound examination is performed by an experienced operator to obtain reliable diagnostic information.

There are no comparative studies with other non-invasive diagnostic methods, but it is now known that this test is the first level exam in the instrumental diagnosis of AVMs.[35]

Magnetic resonance imaging

Magnetic resonance imaging (MRI) study applied to the study of arteriovenous malformations allows excellent typing capacity (so-called diagnostic confidence) and overall balance both in terms of spatial resolution and extension. Unlike what has been observed in low-flow lesions, AVMs are generally characterized by a dark signal in the T1w and T2w sequences (called flow voids) and a lower degree of contrast enhancement (CE) after administration of contrast medium. There are quantitative MRI sequences for the determination of the volumes of shunts and new generation dynamic sequences capable of analyzing the flow characteristics (dceMRI). The anatomy and distribution of the vessels and the nest are clearly visible with the various MR angiography sequences, possibly even avoiding the use of contrast medium (ASL sequences). Currently, 4D MRI angio sequences are also available and they provide images that can be superimposed on those obtained from a traditional angiographic examination, making the latter generally obsolete when not aimed at interventional maneuvers.

The MRI technique is the most frequently used in the overall budget of AVMs.[36-41.]

CT scan

Computed tomography (CT) examination provides better spatial resolution than MRI but lower contrast resolution. The CT angiography study (which uses the administration of iodinated contrast medium in pump and volumetric acquisition in a short time) allows the morphological study (also 3D volumetric) of the nidus as well as the distribution of the afferent and efferent vessels; this method provides useful anatomical indications in the suspicion of bone involvement or venous dilatations and venous aneurysms.[40, 42, 43] It is generally less used than MRI.[35, 40]

The indication to undergo an AngioTC must be placed with extreme caution in women of childbearing age and in pediatric age, due to the secondary risks linked to the exposure to ionizing radiation.

MRI and CT are both used for AVM diagnostics; personal preferences or the need to acquire specific data lead to a choice between the two methods. Only in exceptional cases both exams are performed.

Nuclear medicine

The scintigraphic methods, total body angioscintigraphy (WBB-PS), and the microspheres perfusion test (TLPS) have their usefulness to obtain some specific data on AVMs.

Total body angioscintigraphy (WBB-PS), which consists of the intravenous injection of labeled erythrocytes and evaluation of their distribution by gamma camera, is useful for identifying non-evident areas of AVM, assessing their extent and also to visualize the radicality of an intervention or procedure, as well as the evolution over time of the AVM.[44]

The perfusion test with microspheres (TLPS) involves the injection of albumin microaggregates (or "microspheres") labeled with technetium-99 into an artery upstream of the AVM to be studied and the evaluation of tracer accumulation in the lungs by means of a gamma camera. In a normal capillary circulation, the passage of the microspheres through the capillaries and their arrival in the lungs is negligible, because they are retained in the capillaries themselves due to their diameter, greater than the capillary lumen, while in the case of AVMs the microspheres reach the lungs in a quantity proportional to the shunt extent. This method allows to quantify the volume of the AVM as well as to evaluate the degree of success of an intervention or procedure.[45, 46] This method is practicable only on the limbs.

Arteriography

Finally, selective and superselective arteriography is no longer performed for diagnostic purposes except for selected cases, because MRI and CT provide sufficient data and are not as invasive as arteriography. It can be performed simultaneously with embolization procedures.[47]

Plain radiography

A simple radiographic examination allows to study the bone morphology and its possible involvement in the malformation. Localization of intraosseous AVM nests can be suspected by specific signs of bone structure alteration, especially in the limbs.[48]

Histology

AVMs are vascular malformations consisting of a tangle of arterial, venous and small vessels with an undefined structure, the latter having a lumen of variable dimensions and a wall consisting of smooth and connective muscle tissue. In the context of AVMs, connective tissue and fibro-adipose tissue are interposed. Arteries are often tortuous and veins are modified due to frequent hypertensive damage with thickening of their walls (arterialization); moreover, small vessels with endothelial mitotic activity may be present in variable numbers, evident up to simulating hemangiomas; deposits of hemosiderin can also be observed.[49, 50]

It is possible to distinguish arteries from arterialized veins by the different disposition of elastic fibers, recognizable with specific colors.

Immunocytochemical staining for WT-1 is often positive in AVMs and negative in other vascular malformations.[51]

The Yakes Classification (consisting of four types) has been recently modified, adding a variant of type IV AVMs, characterized by draining fistulas on the venous part of the capillaries and on dilated venules (subgroup of AVMs with capillary-venous microfistulas).[52]

Choice of diagnostic procedures

The choice of the type of investigation to be performed generally follows the principle of proceeding from the least invasive to the most invasive examination. The preliminary examination that provides useful data and allows you to immediately distinguish an arteriovenous malformation from a venous or lymphatic one is the continuous wave Doppler (CW), which in the pocket version represents a simple and rapid instrument [53]. The echocolordoppler allows then to confirm the diagnosis by recording flow signals and to obtain initial information regarding the localization and the extension of the AVM. However, the operator must be familiar with the echocolordoppler study of AVMs.

Question 1
In patients with a clinic suggestive of arteriovenous malformation, the Doppler ultrasound is the most suitable first level examination to evaluate the morphological and haemodynamic characteristics of the malformation?

INTERPRETATION OF THE DATA

To answer Question 1, a consensus statement [54] and four narrative reviews of the literature [32,36,40,45] were identified.

The conclusions of the analyzed studies are consistent with each other. Experts agree in indicating the echocolordoppler as a first level instrumental examination for AVMs, as it allows an initial, rapid and non-invasive evaluation of the main characteristics of the arteriovenous malformation: extension, hemodynamics, tissue infiltration and morphology. The investigation is completely risk-free. The impact on the patient is minimal, as it is a non-invasive assessment. The feasibility is good in the entire national context but, being an operator-dependent examination, it should be performed by experienced personnel in the field. The main limitation of this examination is when it is performed by an operator with little experience in AVMs. The cost is significantly lower than other more complex investigations. Using echocolordoppler as a first exam avoids unnecessary invasive tests.

The studies are relevant to the target population and show no possible bias.

Recommendations
In patients with a clinic suggesting the diagnosis of an AVM, it is indicated to perform the Doppler ultrasound as a first level examination, in order to evaluate the morphological and hemodynamic characteristics of the malformation.
Strong recommendation in favor, level of evidence 4

Once the arteriovenous form and its location have been ascertained, we generally proceed with imaging examinations that more clearly define site, extension, tissue infiltration and morphology of the AVM, according to the classifications of Chou and Yakes (see above). This last data, while not always easily deducible from the imaging examination, is useful though to decide a therapeutic strategy in case of an endovascular treatment. MRI and CT generally provide adequate and sufficient data for a complete diagnosis. The 3D elaborations of the exams add further diagnostic elements, even if they are not mandatory. There is a greater personal preference of the authors for MRI.[40]

Angiography with arterial catheterization, while once was a fundamental examination, is now considered not indicated as a first-choice examination, both because of its invasiveness and because MRI and CT are now able to provide sufficient data. Angiography should be limited to particular cases or as a contextual examination.

Question 2
In patients with Doppler ultrasound suggestive of arteriovenous malformation, what are the second level instrumental examinations most suitable to provide an adequate preoperative evaluation of the malformation?

INTERPRETATION OF THE DATA

To answer Question 2, a consensus statement[54] and six narrative reviews[36, 39, 40, 41, 63, 68] were analyzed.

The studies agree on the execution of an MRI or a CT scan with contrast medium as a second level instrumental examination. Both investigations allow to complete the diagnostic evaluation of AVMs in terms of extension, involvement of surrounding tissues and internal organs and morphology of the AVM type according to the classifications of Chou and Yakes.[3, 4] The 3D elaborations of the exams add further diagnostic elements, even if they are not mandatory. There is a greater personal preference of the authors for MRI.[40]

The examination does not involve significant risks and has an acceptable impact on patients, considering the need of execution for the intervention purposes. It is easily implemented throughout the country, but the interpretation of the images should be performed by radiologists with expertise in the field.

Studies are highly relevant to the target population. The conclusions are consistent and there are no potential biases.

Recommendations
In patients with color Doppler ultrasound suggestive of arteriovenous malformation, it is also indicated to perform an imaging examination as a second level examination, in particular MRI or CT with contrast medium, for a correct preoperative evaluation.
Strong recommendation in favor, level of evidence 4

Generally, no further examinations are indicated, except for specific cases of particular localizations, where further data may be necessary. Peculiar locations, however, can request specific investigations to recognize particular risks. This is the case of localization at the laryngeal or tracheal level, where there is a risk of hemorrhage during intubation if there are exuberant malformations or a risk of post-treatment edema if an embolization is performed. In those cases, a laryngoscopy is indicated.

Treatment

AVMs are considered the most difficult group of vascular malformations to be treated.[55, 56] Despite having different therapeutic possibilities available, the treatment of AVMs is considered particularly difficult and controversial due to the extreme variability of cases, the complexity of the lesions, the considerable technical difficulties of the treatment, the frequent relapses and the high risk of clinical worsening after therapy, not only in the case of incomplete procedures.[53, 56, 57] The complexity of certain injuries also carries an increased risk of complications during and after treatment.

In consideration of all these factors, the indication for intervention must be well thought out. Some authors argue that every patient should be treated to prevent changes that increase the difficulty of treatment.[58] However, considering that a good part of patients in the 1st and even the 2nd Schobinger stage do not show significant medium-term evolution (5-6 years), [35] we tend to avoid intervening in these cases.[40, 53, 54, 59, 60] However, treatment may also be indicated in some cases at the 1st and 2nd stage of Schobinger if there is a marked dysmorphism or other situations that cause an important conditioning of the quality of life, also from a psychological point of view. The indication for treatment is, however, peremptory in stages 3 and 4 of the Schobinger Classification. The appearance of ulcers, a sign of significant worsening, is one of the most difficult conditions to treat.[61] A staging was proposed to be useful for a therapeutic orientation; the proposal still has to be validated by adequate case studies.[62]

Question 3
In patients diagnosed with stable, asymptomatic or oligosymptomatic AVM, or with difficult access sites, are conservative treatments appropriate to replace invasive treatment?

INTERPRETATION OF THE DATA

To answer Question 3, an international consensus[54] and four descriptive papers[40, 50, 58, 60] were analyzed.

Most authors agree with the indication for conservative treatments in the asymptomatic or oligosymptomatic forms of AVMs. The wait-and-see attitude in these cases has the advantage of proposing the solution with less risk and avoiding unnecessary interventions; however, there is the likelihood that waiting will lead to a worsening, even sudden, resulting in a more complex condition to treat. Due to this possibility, some authors propose an early intervention, especially if the treatment appears to be of acceptable difficulty or if a sudden worsening could create a situation that is difficult to treat. This strategy does not harm the patient provided that he is treated promptly in the event of worsening with symptoms' appearance.

The feasibility is good throughout the national territory.

The impact on the patient is good and is generally well accepted, but he must be informed of the possibility of sudden and unpredictable worsening.

The quality of the evidence, assessed through the checklist for systematic reviews, was found to be acceptable. The analysis of the studies highlights a clear relevance for the target population, consistent conclusions and the absence of potential bias.

Recommendations

Conservative treatments should preferably be prescribed in case of stable clinical picture, asymptomatic or oligosymptomatic patient and in case of localizations that make treatment difficult or high risk.

Weak recommendation in favor, level of evidence 3-4

Treatment is based on the following options: medical therapy, surgical treatment, embolization by arterial or venous catheterization, percutaneous alcoholization and laser treatment. One of the major difficulties in the choice of treatment is the extreme variability of cases for which the strategy, the type of technique to be used and the timing can be difficult if not impossible to code in a generalized way and must be decided on a case-by-case basis. A strategy based on a combination of techniques to be performed in stages is often indicated.[63, 64] An embolization followed by a surgical resection within a few days is a strategy used quite frequently.[54, 65] However, depending on the case, other techniques can be combined, even in different chronological order, such as percutaneous alcoholization and laser. The combination of polidocanol sclerotherapy and embolization has been proposed as well as a therapeutic strategy.[66] Not rarely, the result of a treatment can influences the choice and timing of the subsequent treatment.

The operator's experience often represents a determining factor in the choice.[67] Another important element is the involvement of other specialists in the treatment as part of a multidisciplinary strategy.[68] However, multidisciplinarity is not mandatory and it depends on the characteristics of the individual case.

Regardless of the type of technique, it is believed that the simple occlusion of those vessels afferent to the AVM without the elimination of the nest, using different techniques, is burdened by a high relapse incidence, due to the early dilation of collaterals that supply the AVM. The result is a worsened situation because the rehabilitated collaterals are generally more tortuous and less suitable for endovascular treatment. There are various publications of occlusions and/or ligation of afferent vessels with extensive occurrence of relapses from the development of collaterals; however, these are only case series papers.[69, 70]

Medical treatment

Medical treatment still plays a modest role in the treatment of AVMs. Several drugs have been tested but without significant results.

Scientific research in recent years has made it possible to identify the gene mutations underlying numerous vascular malformations. The availability of drugs that selectively inhibit the effects of these mutations greatly expands the therapeutic horizon. The process of employing a drug based on a molecular diagnostic step is called "theranostic."

In the context of vascular malformations, the most studied example concerns rapamycin (Sirolimus).[71] In fact, in various low-flow malformations, the mutation at the base causes the hyperactivation of the mTOR pathway which rapamycin selectively inhibits producing a clinical benefit. It was assumed that AVMs could also respond to rapamycin treatment, but this did not occur (intuitively, since the genetic and molecular basis are not related to low-flow malformations).[72-74] Starting from general pathophysiological assumptions concerning angiogenesis, some drugs have been used in the treatment of hereditary hemorrhagic telangiectasia (HHT), such as Thalidomide and Bevacizumab. Bevacizumab is an anti-VEGF monoclonal antibody, and the effect of Thalidomide is also thought to depend on an inhibition of VEGF as well as TGFa. Both have shown excellent results in reducing the frequency and intensity of epistaxis episodes, typical of HHT. However, these drugs have not shown convincing results in the treatment of AVMs. Recently mutated genes in AVMs have also been identified: BRAF, MAP2k1 and much less often RAS, PTEN and AKT.

BRAF (V600E) and MAP2k1 are also responsible for a certain number of cases of malignant melanoma and in order to improve the clinic of the latter, selective inhibitory drugs (Vemurafenib and Trametinib, respectively) have been developed.

Although therapeutic roles in AVMs have been proposed for several of these drugs on a theoretical[75] or experimental[76] level, there are still insufficient data in the literature to demonstrate their real efficacy. Currently, their use is only off-label and compassionate.

Surgery

The *en-bloc* surgical removal of the malformation was the only treatment option for years. The chances of definitive

success are linked to the radical nature of the surgical excision. Due to the extreme variability of site, extension and infiltration of the tissues, the intervention can be relatively simple in circumscribed and superficial cases but also extremely demanding in diffuse forms, infiltrating the tissues and in sites with complex anatomy, such as the face, the hand, the neck, the pelvis and others.[77, 78] Involvement of noble structures, such as nerves, can further complicate an AVM surgery due to the difficulty in isolating them from the malformation without causing damage. The removal of infiltrating AVMs can in many circumstances involve an extremely destructive act and, in extreme cases, severe bleeding.[54, 79] Blood losses can be minimized with the use of pneumatic tourniquets in peripheral locations and with the use of hemorrhoids. To reduce intraoperative risks and increase the chances of success, it may be useful to perform interventions in a team with a specialist in the affected area. The chances of success are greater in the rare cases of circumscribed AVM and in the more frequent cases of intramuscular AVM. To increase the chances of success with greater radicality, in selected circumstances, after extensive demolition of compromised tissues, reconstruction with grafts, the packaging of free vascularized musculo-skin grafts or the use of skin expanders can be considered.[80] Partial removal, especially in children or adolescents, can lead to a worsening of the clinical situation. Combination with embolizations is a strategy used with one certain frequency, even if it is not always indicated or possible.[65] Despite all of these risks and technical problems, surgical treatment may be the only viable therapeutic option in particular cases and also prove to be a life-saving solution. For specific localizations, the elaboration of work protocols can be useful, considering however that exceptions are always possible.[81]

Embolization

The treatment of AVMs by embolization consists in the closure of the nidus and the fistulas that constitute it by means of an endovascular approach (arterial or venous).

Embolization by arterial catheterization involves the occlusion of the AVM nidus by placing different substances in the transition area between the pathological arteries and veins (characterized by different degrees of arterialization). This delivery takes place through an endovascular microcatheter that has been brought closer to the pathological target by means of larger coaxial catheters.

In particular situations, the approach to the nidus can be analogously obtained in a retrograde way using a venous catheterization technique.[59, 82]

These endovascular procedures can be used as the only therapeutic method (stand-alone therapy), but most of the time it is performed in combination with other treatments such as surgery, percutaneous occlusion, laser etc.

The wide variability of clinical situations and the increasingly broad spectrum of embolizing material available require not only an effective but also a continuously updated technique.

Endovascular embolization is considered the first-choice therapeutic method for extensive or surgically inaccessible AVMs. Even with the same reservations expressed regarding surgery and the worsening effects in the event of partial closure of the nidus, embolization is also allowed as palliative therapy in order to stabilize or slow down the progression of symptoms. The best chances of success with endovascular treatment are in AVM type I and II (arteriovenous and arteriolo-venous) and minor with type III (arteriolo-venular) forms of the Cho classification.

The risk of iatrogenic damage during embolization increases exponentially in the treatment of pathologies localized in acral regions (hands, feet, forearms, nose, auricles, etc.). In particular, at the level of the hand, embolization involves the risk of complications (such as necrosis and nerve damage) and can be used by expert hands by carefully selecting the indication.[83]

Embolizing materials can be roughly divided into two categories:

1) solids, among which the main ones are:
   - coils (spirals);
   - PVA particles;
   - plug;
2) liquids, the main ones being:
   - adhesives (type NBCA);
   - non-adhesive (EVOH, at the base of various commercial preparations such as Onyx, Squid and Phil);
   - pure ethanol.

Some materials such as alcohol-polyvinyl chloride (PVA) particles are rarely used due to the temporariness of the closure (the microspheres are removed by the monocyte-macrophage immune system), relegating their use to other pathological conditions. They also not infrequently pass-through fistulous shunts and reach the pulmonary bed. Furthermore, the use of very small diameters not rarely causes ischemic lesions of the periwound regions (for example the skin).

Even the spirals (Coils) are rarely implanted as they determine a proximal occlusion of the afferent vessel without excluding the "nest," thus determining an important stimulus to reactive neoangiogenesis and hindering any subse-

quent endovascular treatments. Their use is proposed for the closure of the venous efferent vessels of type II AVMs (arteriolo-venous), especially in embolizations with ethanol.[84]

NBCA (known as cyanoacrylate glue, type Glubran 2) is one of the most widely used materials; it has the characteristic of penetrating into the fistulous bed (capacity which can be modulated by variations in the volume of its radiopaque oily solvent) allowing it to reach the nest; this ability is given to it by the pharmacodynamic features characterized by a progressive polymerization in contact with the blood during migration. If the viscosity is not optimal, the risks of passage of the material into the pulmonary circulation or proximal arrest of the cast are not negligible (there is also the possibility that the same microcatheter used for the release may be glued). Other possible complications such as the inflammatory reaction linked to polymerization and paradoxical embolization, make the use of cyanoacrylate a technique that can be used by expert operators.

The non-adhesive material (EVOH), widely used in interventional neuroradiology, is a cohesive material able to determine a very consistent "cast" of the nest by polymerization. Its use in extended AVMs is controversial both for its high costs and for the risk of inducing neoangiogenesis; it is burdened by non-negligible risks of paradoxical embolization (mainly determined by the "stop and go" technique, with consequent resumption of injection in a blocked flow condition). Like the glue, it is especially recommended in presurgical procedures.[85, 86]

Finally, ethanol (used in the form of absolute alcohol at 98%) has for many years been considered the most effective embolizing agent due to the "first-pass" effect, that is the ability to destroy the endothelium during the passage through the nidus. This denaturing effect determines the elimination of the pro-angiogenic receptor component expressed in the membrane and a complete destruction of the AVM nest.[87, 88] The advantage of this effect is the complete occlusion of the vessel and the inhibition of the secretion of new angiogenic factors that stimulate neoagiogenesis.[87] Complications in the use of ethanol are site-specific and volume-specific, with considerable variations: transient hemoglobinuria, adjacent tissue necrosis (skin, primarily), neurolysis (lesion of peripheral nerves possibly incorporated by the AVM) and the sudden modification of cardio-respiratory parameters (vasodilation, bradycardia, pulmonary hypertension), particularly evident in pediatric subjects. The latter can be minimized both by respecting the maximum administrable volume (1 mL/kg),[89] and by fractioning the boluses (max. 0.14 mL/ethanol/kg). [90] The most recent reports, unlike the older ones, show that complications of alcohol treatment are rare, especially if performed by personnel with extensive experience.[91]

The rapid spread of injected ethanol can possibly be minimized, if necessary, by:

- manual compression of the efferent veins, where possible;
- reduction of "backward" flow with balloon catheter;
- occlusion of discharge ways by means of coils or pneumatic tourniquet.[40] In the case of superficial AVMs (especially those of type III, arteriolo-venular), percutaneous injection into the nest may be indicated.

Percutaneous alcoholization

In addition to the use of ethanol for catheter embolization, the direct percutaneous puncture technique of the AVM area can be used to introduce ethanol. The introduction of the needle and the control of correct positioning can be guided by intra-procedural Doppler or Echo Doppler or by angiographic control by injecting contrast into the needle itself when reflux appears. The procedure can also be performed for localizations in particular sites, such as the peri orbital region,[92] the tongue.[93] the nose and the intraosseous sites; in the latter it can be combined with the application of spirals during the procedure itself.[94, 95]

Also for this technique, as for that of transcatheter alcoholization, it is recommended not to exceed the maximum dose of 1 cc/kg, divided into several injections. Other authors recommend lower total doses (0.4-0.5 mL/kg). The complications of this technique are less serious than initially thought and are the same as for catheter treatment: transient hemoglobinuria (rare and regressing without results), skin necrosis (in rare cases, even extensive), nerve lesions (very rare and generally temporary), muscle contractures (in case of treatment of intramuscular AVM), pulmonary hypertension.[91, 94, 95] In very rare cases there has been an exitus. The evolution towards necrosis during the procedure itself is unpredictable because no signs of skin distress are visible at the moment. These generally appear after a few hours (areas of "leopard spot" cyanosis): the actual necrosis occurs after a few days. The area of necrosis is delimited and heals with appropriate dressings. In the case of necrosis, the result is often an extensive, even complete, occlusion of the AVM. The importance of a good experience in the methodology of the person performing it is emphasized, which significantly reduces complications.

Laser

The laser treatment, superficial or intralesional, can be useful to occlude limited areas of AVM of modest size in a targeted manner. The technique involves the use of a fiber that can be applied in the context of the AVM both superficially and percutaneously at the interstitial level. The use of an ultrasound Doppler as a guide to accurately identify the site of deep AVMs may be useful.[98, 99] There is also the theoretical possibility of applying targeted treatment by introducing the fiber into a catheter.[98, 100]

Cryotherapy

Treatment by percutaneous cryotherapy in residual AVMs after embolization treatment in the craniofacial region has recently been proposed. Publication is limited to 4 cases and requires further validation.[101]

Question 4
What treatments are effective in arteriovenous malformations?

INTERPRETATION OF THE DATA

To answer Question 4, an international consensus of experts,[53] a guideline,[83] eight own case studies[59, 65, 66, 82, 88, 91, 95, 96] a systematic review,[87] and four discursive works were analyzed.[40, 94, 98, 99]

The authors agree on the views on the effectiveness of the individual techniques. They also agree on the individuality of the therapeutic program to be proposed to the single patient due to the great variability of location, extension and evolution of the disease. There are no comparative studies on the different techniques; each author illustrates his own case studies with the techniques at his disposal. The analysis of the studies concludes that a specific therapeutic strategy must be chosen for each patient, by means of an intervention among those listed or even a combination of these. Even the timing, in the case of multiple interventions, must be decided on a case-by-case basis. The careful therapeutic choice must aim at the best relationship between risks and benefits. The aim is to achieve complete occlusion or removal of the AVM nest. The ideal outcome is the disappearance of the pathology. If the occlusion or removal cannot be completed, the goal is a partial reduction with significant improvement of the symptoms. The damage of the different interventions can be various: ischemia, a variably extended necrosis, nervous deficit (very rare) or a sudden worsening of AVM due to an activating phenomenon linked to the intervention. In some cases, severe bleeding can also occur. However, this phenomenon is unpredictable.

If effective, the intervention is aimed at eliminating the pathology and the symptoms or at reducing them significantly. This will lead to an important improvement in the patient's quality of life. The complications, which are difficult to predict, can also lead to a worsening of the patient's condition. In the event of a major deterioration, it could lead to amputations.

The various procedures are technically feasible in most of the national territory. However, both for a choice of the type of treatment and for its execution and also for the timing of combined procedures, it is recommended to perform them in a dedicated center or in any case with good multidisciplinary experience in the treatment of AVMs. Such centers are currently very rare in our country and also abroad.

Studies are relevant to the target population; conclusions are consistent and no possible bias are found.

Recommendations
Given the great variability of AVMs, the choice of therapeutic technique must be made specifically for the individual case. If useful and necessary, combinations of techniques can be employed.
Recommendation of good clinical practice, based on the experience of the panel

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Guidelines for complex vascular malformations

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Introduction

Definition

In the wide spectrum of vascular malformations, traditionally classified according to histological criteria integrated with hemodynamic criteria (1996 ISSVA XI Workshop-Rome), a particular place is occupied by a group of malformations defined Complex Vascular Malformations (CVM) or Syndromic Vascular Malformations. Nosological classification of these conditions has been re-examined considering recent genetic acquisitions.[1]

They are characterized by some peculiarities:

- possible coexistence of 2 or more different histological components (combined malformations);
- possible multiple or disseminated localizations, with skin components associated with visceral components;
- possible coexistence of non-vascular anomalies;
- genetic connotation ascertained or being defined. Sporadic onset due to somatic mutation or hereditary transmission.

Some complex malformative pictures are traditionally framed as Syndromes, defined in some cases with eponyms (*e.g.* the Klippel-Trenaunay Syndrome), while in others, more recently acquired, with acronyms (*e.g.* the PROS Syndrome).

The use of traditional terminology applied incorrectly has been and still is a source of confusion and ambiguity also due to the overlap of some clinical features. The correct redefinition and interpretation of the distinctive criteria of these pathologies is therefore essential in clinical practice, not only for the purposes of prognosis, therapeutic strategy and treatment timing, but also for correct counseling with the relatives of affected patients.[2-4] Recent studies have in fact highlighted the unreliability of cases in which the distinctive criteria between the Syndromes had not been correctly applied.[5, 6] The vascular anomaly in these malformative pictures may not be the priority.[7] A common element in many Syndromes is bone or other tissues hypertrophy with secondary gigantism defined as *overgrowth*.

Question 1
What is the recommended clinical path for the correct diagnostic classification and certification of rare disease in the vascular complex malformations?

Recommendation of good clinical practice, based on the experience of the panel: GGP grade. It is no supported by scientific evidence due to the absence of studies in literature**.**

Diagnostic recommendations

- Due to the complexity and rarity of the syndromic patterns, it is indicated to refer the patients to a Reference Center specialized in Vascular Anomalies for the diagnostic work out.
- At the request of the Specialist, it is indicated to complete the clinical-anamnestic examination with targeted noninvasive radiological and diagnostic investigations (*e.g.*, Echocolordoppler, X-Ray, MRI, angio-CT, lymphoscintigraphy). The recommended timing for some instrumental investigations may differ based on the need to perform such investigations in anesthetic sedation during the pediatric age.
- Genetic counseling and genetic-molecular tests on biopsy sampling of pathological tissue and/or peripheral blood could be indicated for the purpose of correct classification and certification of the rare disease.
- It is indicated that the histopathological examination of the material taken during surgical procedures is analyzed by expert personnel for the correct reporting and classification of the vascular anomaly.

Recommendations of good clinical practice, based on the experience of the panel: GPP grade

Question 2
What is the recommended clinical path with the aim of a proper therapeutic management of the vascular complex malformations?

Recommendation of good clinical practice, based on the experience of the panel: GGP grade. It is no supported by scientific evidence due to the absence of studies in literature.

Treatment/management recommendations

• Therapeutic indications cannot be standardized for patients with CVM: it is indicated that for each patient an individual therapeutic plan is drawn up on the basis of the clinical picture complexity and of the anatomical districts affected by the malformation.

• A multidisciplinary management is indicated in collaboration with all the Specialists involved for the different affected anatomical areas.

• It is recommended to perform early interventional procedures with the purpose of maintaining the patient's quality of life and preventing and/or containing spontaneous progression of the malformation.

• A multidisciplinary management is indicated, exploring all possible treatment strategies.

• In the presence of secondary clinical symptoms and/or clinically evident and worsening deformities, not responsive to standard treatments, the use of new systemic *targeted therapies* administered off-label could be indicated.

• In the presence of clinically relevant chronic pain/functional deficit/dysmorphism, a psychological support is indicated.

• For the families of patients suffering from Syndromic Complex Vascular Diseases, it could be indicated to register with an association that groups the families of patients suffering from the same disease (where present) in order to obtain a psychological benefit and support in finding useful information for the management of the disease.

Recommendations of good clinical practice, based on the experience of the panel: GPP grade

Classification

Complex malformations can be divided into 2 large groups, as shown in Table I.

Distinctive criteria: clinical, epidemiological and therapeutic criteria of group A syndromes

The first six conditions listed in Group A fall under the *PIK3CA* gene mutation pathology chapter.

PIK3CA-related overgrowth spectrum (PROS)

The acronym PROS, *PIK3CA*-Related Overgrowth Spectrum, includes a group of congenital or early onset conditions with a very heterogeneous phenotype, characterized by the presence of activating, somatic pathogenetic variants of the *PIK3CA* gene conditioning segmental or "mosaic" overgrowth. In the presentation spectrum of PROS, two groups are distinguished based on clinical criteria: the PROS-A group (in which two or more congenital anomalies are associated) and the PROS-B group (in which only one isolated anomaly is present).[3] The spectrum of congenital anomalies characterizing PROS-A group includes: segmental overgrowth, vascular malformations (capillary, venous, arteriovenous, lymphatic) and epidermal nevus. Onset of pathogenetic variants in *PIK3CA* gene (gain of function mutations) leads to an increase in enzymatic activity of phosphatidylinositol 3 kinase (PI3K) with consequent dysregulation of *PI3K-AKT-mTOR* signaling pathway and secondary effects on cell growth, apoptosis and angiogenesis.[8] Somatic mutations by definition are random and occur after conception, involving only a part of the subject's tissues. The term somatic mosaicism refers to the presence in the same individual of two cell populations that are genetically distinguished, derived from a post-zygotic mutation: a cell line is affected by the mutation and a cell line is devoid of it. These mutations do not involve the germline, as demonstrated by the fact that mutations are detected in tissue samples affected by the malformation, but they are absent in peripheral blood of the same patient, or in other tissues not affected by the malformation.

Mosaic mutations of *PIK3CA* gene are associated to different clinical pictures which however share some main characteristics:

• congenital or very early childhood onset;
• sporadic and non-inherited transmission;
• mosaic pattern of distribution;
• overgrowth which can involve different tissues: bone and/or soft tissues (muscle, adipose tissue, skin, nervous tissue);
• the severity of hypergrowth can range from the involvement of a single district (*e.g.*, macrodactyly) up to the gigantism of an entire hemisome;
• the cutaneous manifestation of mosaicism can determine the formation of a capillary malformation and/or an epidermal nevus.

PROS-A spectrum includes the following conditions:

• Klippel-Trenaunay Syndrome;
• congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal (CLOVES) Syndrome;
• CLAPO (lower lip CM - face and neck LM - asymmetry and partial/generalized overgrowth);
• FAVA (fibroadipous vascular anomaly);
• diffuse capillary malformation with overgrowth (DCMO);

• megalencephaly-capillary malformation (MCAP or M-CM);
• fibroadipose hyperplasia or overgrowth (FAO);
• hemihyperplasia multiple lipomatosis (HHML);
• fibroadipose infiltrating lipomatosis/facial infiltrative lipomatosis;
• dysplastic megalencephaly (DMEG).

The first six conditions in the list, which are classified as PROS-A and fall under the chapter of CVM (Group A) will be described in detail below.[9]

For some malformations of PROS have been described an increased incidence of Wilms[9] during the first years of life.

Question 3
Is there an increased incidence of cancer in patients with PROS Syndrome?

Since there are not enough publications to answer this Question, the decision whether or not to undertake oncological surveillance is left to the clinician on the basis of the genetic data and clinical characteristics of the patients.

Recommendation
In patients with a clinical and/or molecular diagnosis of PROS, periodic ultrasound screening is indicated for the purpose of oncological surveillance.
Recommendation of good clinical practice, based on the experience of the panel: GPP grade

RASA1-related disorders

Parkes Weber Syndrome (PKWS, group A) and the capillary-arteriovenous malformation Syndrome (CM-AVM, group B) fall under the category of *RASA1-related disorders*.

The protein encoded by *RASA1* gene is involved in vascular development as a regulator of cell proliferation and differentiation.[10]

Mutations in heterozygosity of *RASA1* gene are causative of CM-AVM with an autosomal dominant inheritance mode, while in the PKWS Syndrome the mutations identified are somatic/mosaic. The PKWS Syndrome phenotype is mainly characterized by the presence of an extensive cutaneous capillary malformation, affecting one extremity associated with its overgrowth due to involvement of bone and soft tissues, and by the presence of arteriovenous lesions.[10]

The main clinical features of CM-AVM Syndrome, instead, are the presence of multifocal cutaneous capillary malformations associated, in about 30% of cases, with high flow vascular lesions (arteriovenous malformations) that can affect cutaneous, subcutaneous, intramuscular, bone and cerebral districts.[9]

Recently, the genetic mechanism based on the second hit has also been proposed for CM-AVM Syndrome, to explain its phenotypic heterogeneity. For some of these patients, the presence of the heterozygous mutation in the germ line has been demonstrated in combination with a second somatic mutational event, involving the normal allele, in the vascular lesion (second-hit hypothesis).[11, 12]

Finally, in 2019 Gordo *et al.* described two patients with a clinical diagnosis of CM-AVM and constitutional mosaicism for *RASA1* defined as the presence of a mosaic variant in all cell types of the same individual. However, further studies will be necessary to confirm this hypothesis.[1]

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Klippel Trenaunay Syndrome

Definition

Klippel Trenaunay Syndrome (KTS) is a complex vascular malformation of the capillary-venous-lymphatic system, which affects one or more limbs with possible extensions to the trunk, genitals, pelvis and visceral organs. KTS is more frequently unilateral (85-95% of cases) and mainly involves the lower limb (90% of cases). It is characterized by the association of anomalies of the skin, subcutaneous, muscular and osteo-articular tissues: skin lesions (capillary malformations, angiokeratomas), anomalies of the superficial and sometimes deep venous circulation (atypical superficial varices, chronic venous insufficiency, atresia), hypertrophy o hypotrophy of the involved limb, lymphedema.

If peripheral arteriovenous micro-shunts are present in the affected area, the clinical picture is configured as "Klippel-Trenaunay-Weber" or "Parkes-Weber" Syndrome.

Epidemiology

KTS is estimated to affect at least 1 in 100,000 people worldwide. In most cases it is a sporadic disease with no predilection for sex or ethnicity. It is included in the list of rare diseases.

Etiopathogenesis

Klippel-Trenaunay Syndrome is a genetic-based disease, belonging to the group of conditions defined as "*PIK3CA* Related Overgrowth Spectrum" (PROS). It is caused by gain of the function mosaic mutation in *PIK3CA* gene. These pathogenetic variants result in activation of the enzymatic activity of phosphatidylinositol 3 kinase (PI3K) resulting in dysregulation of the PI3K-AKT-mTOR signaling pathway and secondary effects on cell growth, apoptosis and angiogenesis.[1, 2]

Clinical aspects

KTS is characterized by the following diagnostic triad:

• capillary skin malformations that extend to almost all of a lower limb (more rarely the upper one), with geographical distribution, respecting the median line, often associated with hypertrophic angiokeratomas or superficial lymphatic microvesicles with a typical "*salmon egg*" appearance;

• abnormalities of the superficial and/or deep venous circulation: varicosities or superficial venous ectasias, persistence of the marginal embryonic vein of Servelle (present in 55% of cases), atypical perforating veins, atresia/hypoplasia of the deep venous circulation. Varicosities are present in up to 95% of cases, usually appear on the lateral side of the affected limb and can be responsible for the onset of serious complications such as venous thromboembolism;

• hypertrophy (gigantism) of the limb affected by the vascular malformation with consequent functional dysmetria.[3] Conversely, hypotrophy of the affected lower limb is more rarely observed (Servelle-Martorelle phenomenon).

In 30% of cases there is an intrapelvic extension involving the visceral organs, in particular the descending colon, the sigmoid and the rectum, as well as the urethra and bladder. Visceral involvement usually manifests as intestinal or bladder bleeding. Visceral pelvic involvement in women is a risk factor in pregnancy. The Syndrome has a progressively worsening clinical course during the life of the patients. KTS may be associated with chronic consumption coagulopathy, such as localized intravascular coagulopathy (LIC). It is caused by the local chronic activation of coagulation factors secondary to intralesional venous stasis and is characterized by high values of fibrin d-dimers and hypofibrinogenemia.[4]

Diagnosis

The echo color Doppler of the affected limb represents the first level examination useful for the evaluation of patients with clinical picture indicative of KTS and for the planning of the therapeutic path.

In particular, the echocolordoppler allows:

• to recognize or exclude the presence of anomalies of the superficial and deep venous circulation (atresia/hypoplasia of the deep femoral-popliteal venous axis, persistence of the marginal Servelle embryonic vein, presence of incontinent perforating vein in atypical locations, presence of deep venous incontinence on a dysplastic basis;[5]

• to recognize or exclude the presence of arteriovenous shunts, allowing the differential diagnosis with Parkes Weber Syndrome.

The diagnostic framework in the KTS also makes use of the following exams:[6, 7]

• magnetic resonance imaging (MRI) with contrast medium (allows a better anatomical definition of deep tissues and is fundamental for the study of splanchnic malformations. MRI is a specific diagnostic tool for the study of intra-articular infiltrations);[8]

• comparative radiography (X-Ray) of the limbs (to study and monitor the leg length discrepancy, particularly

during the developmental age. If a functional discrepancy in leg length is present, careful orthopedic follow-up during the developmental age is indicated to correct the defect early by epiphysiodesis or other early corrective interventions, which are preferable to late correction of the discrepancy by the method; Ilizarov);

• genetic counseling and molecular-genetic examination on a biopsy sample taken from the site of the vascular malformation to search for mosaic mutations in the PIK3CA gene;[9]

• gait analysis for the physiatric evaluation of the walking deficit;

• lymphoscintigraphy to superficial and deep lymphatic system study;

• rectosigmoidoscopy and urethro-cystoscopy (these endoscopic examinations are important in case of both intestinal and urinary hemorrhages);

• spirometry/respiratory function tests for early diagnosis of pulmonary hypertension;

• ascending phlebography by distal venupuncture and contrast medium injection is sometimes performed in selected cases for the study of the deep venous circulation.

Treatment

KTS therapy usually involves two options:

• conservative management aimed at treating symptoms, limiting a spontaneous worsening of evolution and preventing complications related to distal venous hypertension (customized elastic compressions,[10] orthopedic aids [insoles] and plantar support to correct the legs length discrepancy,[11] manual lymphatic drainage for the treatment of distal lymphedema. Despite the low level of scientific evidence, elastocompression represents the first choice option to limit the complications of chronic venous insufficiency in KTS);

• invasive therapies (sclerotherapy, laser therapy and surgery);[12]

Invasive therapies in KTS include:

• treatment of superficial dysplastic varicosities and the marginal embryonic vein of Servelle using different methods based on the clinical picture (sclerotherapy; EVLT endovascular laser treatment; ligation and surgical section/stripping) (these procedures are indicated only in case of a patent deep venous circulation. [13] In case of atresia of the deep venous circulation, a careful preoperative evaluation of the compensatory venous circulation is necessary);

• scleroembolization of extratruncular venous malformations;

• transcutaneous laser photocoagulation of capillary malformations, angiokeratomas and "salmon roe" cutaneous lymphatic vesicles;

• epiphysiodesis for the containment of diaphyseal hypertrophy in the hypermetrical limb: indicated in case of discrepancy between the limbs greater than 2 cm.

In case of complex vascular malformation associated with overgrowth, even in absence of symptoms, invasive interventional procedures are indicated to maintain patient's quality of life and to prevent and/or to contain the spontaneous progression of the malformation. Early treatment of dysplastic varicosities of the lower limbs in KTS, performed by surgery or scleroembolization, is effective to prevent thromboembolic events and complications from distal chronic venous hypertension (CVH).[14, 15]

EVLT with 810 nm diode laser represents an effective and safe therapeutic option for the treatment of dysplastic varices in patients with KTS in association with other therapeutic strategies (elastic compression, sclerotherapy, surgery).[16-20]

New pharmacogenetic acquisitions have demonstrated the efficacy of m-TOR pathway inhibitors in PROS Syndromes. Therefore, off-label administration of Rapamycin (Sirolimus) in the treatment of KTS is justified for chronic pain control, for chronic coagulopathy correction and to treat the microcystic lymphatic component.[21]

Complications

The main causes of morbidity in KTS include: superficial (14%) and deep (4%) venous thrombosis, pulmonary embolism (2%),[22, 23] infectious cellulitis (10%), skin ulcers secondary to distal venous hypertension and bleeding from cutaneous angiokeratomas.

The frequent onset of thromboembolic phenomena correlates with an increased risk of secondary pulmonary hypertension (20%) up to the formation of pulmonary arteriolar aneurysms.[24]

Joint involvement, particularly of the knee, can lead to chronic early arthritic degeneration.[25]

Pregnancy in patients with KTS could cause worsening of symptoms and could lead to an increased risk of thromboembolism and *post-partum* bleeding. An antithrombotic prophylaxis is therefore necessary.[26, 27]

In case of clinically relevant chronic pain/functional deficit, psychological support is indicated to treat the psychosocial distress.[28] Psychiatric complications such as depression and anxiety related to pain and disease severity (functional impotence) can affect the quality of life in these patients.[29]

There is no increased prevalence of embryonic malignancies in KTS patients.[30]

Question 1
What are the instrumental investigations necessary for the purposes of the diagnostic classification of patients with a clinic suggestive for KTS?

For the purposes of the diagnostic classification of patients who have clinical findings suggestive of KTS (capillary malformation, hypertrophy, dysplastic varicosities involving a lower limb) it is appropriate to investigate the anatomy of the superficial and deep venous circulation.

The Echo color Doppler examination represents the first-choice instrumental examination as it provides anatomical and hemodynamic information, it is a noninvasive exam, and it also plays a fundamental role in the planning of the therapeutic strategy.

The Echo color Doppler is an operator-dependent exam: therefore, it is desirable that it is performed by an expert operator in the context of a Reference Center for Vascular Malformations.

If the information provided by the Echo color Doppler exam were not diriment, it is indicated to complete the diagnostic procedures with second level instrumental radiological examinations, in particular MRI with contrast medium.

INTERPRETATION OF THE DATA

To answer Question 1, 2 narrative reviews[6, 11] and 1 case series[7] were identified in the literature describing patients with Klippel-Trenaunay Syndrome and which defined that the echo color Doppler of the limb affected by the vascular malformation as first level examination for the purposes of the patient's diagnostic classification. The conclusions of the analyzed studies are consistent with each other.

Experts agree that in patients with a clinic suggestive of SKT it is indicated to perform the Doppler ultrasound of the limb affected by the vascular malformation as a first level examination for the purposes of the diagnostic setting.

The examination is noninvasive and the damage resulting from an incomplete diagnostic classification of the SKT would be greater than the costs deriving from the diagnostic examination necessary for the correct classification. In addition, the examination has significant relevance in the planning of the therapeutic process.

The impact of Echo color Doppler diagnostics is acceptable for patients and family members.

Echo color Doppler diagnostics should be performed in specialized reference structures for the treatment of Vascular Malformations. The studies are relevant to the target population and argue about relevant comorbidities. There are no concerns about possible bias.

Recommendation
In patients with a clinic suggestive of KTS it is indicated to perform the Doppler ultrasound of the limb affected by the vascular malformation as a first level examination for the purpose of the patient's diagnostic classification.
Strong recommendation in favor, level of evidence 3-4

Question 2
Is radiographic follow-up indicated for early correction of the defect in KTS patients with leg length discrepancy?

In the presence of functionally relevant leg length discrepancy, careful orthopedic follow-up is indicated, by means of comparative radiography of the lower limbs, during the developmental age for the purpose of early correction of the defect by means of epiphysiodesis or other early corrective interventions, preferable to late correction of the dysmetria by Ilizarov intervention.

INTERPRETATION OF THE DATA

To answer Question 2, 3 case series[11, 16, 25] and 3 narrative reviews[3, 12, 14] have been identified in the literature which describe the need to perform radiological follow-up during developmental age in order to early detection of limb discrepancies in patients with KTS.

The conclusions of the analyzed studies are consistent with each other.

Experts agree that in patients suffering from KTS with leg length discrepancy it is indicated to perform a careful follow-up by means of a comparative radiographic study during the developmental age in order to identify and treat the defect early.

The examination is not invasive, and the early detection of limb discrepancies allows to optimize the timing of the intervention. The damage of radiographic follow-up derives from exposure to X-rays. The radiological examination can also be performed in children without the need for anesthetic sedation throughout the country. The impact of radiographic diagnostics is acceptable for patients and family members.

Late diagnosis of limb asymmetry would result in a late and suboptimal correction of the defect due to skeletal maturity being reached.

The studies are relevant to the target population and argue about relevant comorbidities. There are no concerns about possible bias.

Recommendation
In the presence of leg discrepancy, careful orthopedic follow-up during the developmental age is indicated by periodic comparative radiography (X-Ray) of the lower limbs for the purpose of early correction of the defect.
Strong recommendation in favor, level of evidence 3-4

Question 3
Is elastic compression an effective conservative therapy in SKT?

Conservative management in SKT is aimed at treating symptoms, limiting spontaneous worsening evolution and preventing complications related to distal venous hypertension. Elastocompression is the first-choice option in the conservative treatment of chronic venous insufficiency and distal venous hypertension.

In the pediatric age, it is necessary to package the elastic compression devices tailored to the extent of the malformation and with a progressive adaptation of the elastic braces to the patient's body growth.

INTERPRETATION OF THE DATA

To answer Question 2, 1 Systematic Review[10] was identified in the literature, which evaluates the benefit of conservative therapy by means of elastic compression in patients with Klippel-Trenaunay Syndrome.

The analyzed review takes in consideration retrospective studies with low level of evidence. The studies analyzed agree on the benefit of conservative therapy. Experts agree in affirming the benefits of conservative therapy: reduction of chronic LIC coagulopathy, improvement of symptoms, reduction of edema and protection from trauma, prevention of complications.

Conservative treatment is free from significant risks and is well tolerated by the patient and family. There are no concerns about possible bias. However, comparative studies would be appropriate in order to verify the effectiveness of the treatment compared to control cases.

Recommendation
Despite the low level of scientific evidence, elastocompression is indicated and represents the first choice option for the containment of the complications of chronic venous insufficiency in KTS.
Strong recommendation in favor, level of evidence 2++

Question 4
Is early treatment of dysplastic varicosities of the lower limbs in SKT indicated for the prevention of thromboembolic events and complications from distal chronic venous hypertension (CVH)?

Early treatment of dysplastic varicosities of the lower limbs in KTS by surgery or scleroembolization is effective for the prevention of thromboembolic events and complications from distal chronic venous hypertension (CVI).

INTERPRETATION OF THE DATA

To answer Question 4, 2 case series have been identified in the literature [13,23] that evaluate the efficacy of early treatment of dysplastic veins in patients with Klippel-Trenaunay with surgery, scleroembolization or EVLT laser in the prevention of thromboembolic complications and chronic distal venous insufficiency. The conclusions of the analyzed studies are consistent with each other.

Experts agree that, in KTS patients with dysplastic varicosities of the lower limbs, early treatment is useful in the prevention of thromboembolic complications and chronic distal venous insufficiency.

The treatment is invasive for the patient, however the benefits obtained in terms of prevention of thromboembolic events and complications related to chronic distal venous hypertension are greater than the damages deriving from the treatment, which are related to surgical ablation techniques (hemorrhages, hematomas, surgical wound infections), scleroembolization (skin ulcers, pulmonary thromboembolism), EVLT (skin burns, nerve damage, iatrogenic arteriovenous fistulas, heat-induced venous thrombosis, deep vein thrombosis).

The treatment has a moderate impact on the patient because it requires hospitalization and sedation. However, it is acceptable for the patient and family members. Both studies are burdened by the small sample size being analyzed which could affect the results in terms of safety and efficacy.

Recommendation
Early treatment of dysplastic varicosities of the lower limbs in KTS by surgery, scleroembolization or EVLT laser is indicated as it is effective for the prevention of thromboembolic events and complications from distal chronic venous hypertension (CVH).
Weak recommendation in favor, level of evidence 3

Question 5
Is EVLT with 810 nm diode laser an effective and safe therapeutic option for the treatment of dysplastic varices in patients with SKT?

INTERPRETATION OF THE DATA

To answer Question 5, 2 case series have been identified in the literature[18, 20] that evaluate the efficacy, safety and feasibility of intravenous ablative therapy by laser of dysplastic veins in patients with Klippel-Trenaunay.

The 2-case series analyzed are consistent in affirming efficacy, safety and feasibility of the treatment.

Experts agree that, in patients suffering from KTS with dysplastic varices and a suggestive clinical frame, endovascular ablative treatment is effective in occluding the aforementioned angiodysplasias in order to improve symptoms. The damage resulting from the treatment can be the following: skin burns, nerve damage, iatrogenic arteriovenous fistulas, heat-induced venous thrombosis, deep vein thrombosis. The complication rate of the treatment is so low that the risk is acceptable compared to the benefits it brings. The treatment has a moderate impact on the patient requiring hospitalization and sedation.

Both studies are burdened by small sample sizes that could affect the results in terms of safety and efficacy.

Recommendation

EVLT treatment with 810 nm diode laser of dysplastic varices in patients with KTS could be indicated as it represents an effective and safe therapeutic option in association with other therapeutic strategies available (elastic compression, sclerotherapy, surgery).

Weak recommendation in favor, level of evidence 3

Question 6

Pregnancy in patients with KTS causes aggravation of symptoms and could lead to an increased risk of thromboembolism and *post-partum* bleeding. Is antithrombotic prophylaxis necessary in pregnant KTS patients?

INTERPRETATION OF THE DATA

To answer Question 6, 1 retrospective case-control study[27] and 1 retrospective observational study[26] were identified in the literature, evaluating the thrombo-embolic risk in pregnancy and the risk of *post-partum* bleeding in women with KTS. There is no agreement in the studies analyzed regarding the increased thrombotic risk in pregnant KTS patients and the increased risk of *post-partum* bleeding in them. However, although with a low level of evidence, prophylactic antithrombotic therapy is suggested in pregnant patients.

The benefits obtained in terms of prevention of thromboembolic events and complications related to chronic distal venous hypertension are greater than the damage related to antithrombotic prophylaxis (bruising and minor bleeding, infection of the injection site).

Both studies are burdened by the small size of the sample being analyzed which could affect the results obtained.

Recommendation

Peri-partum antithrombotic prophylaxis may be indicated in pregnant patients with KTS.

Weak recommendation in favor, level of evidence 2+/3

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CLOVES

Definition

CLOVES is the acronym of Congenital Lipomatous asymmetric Overgrowth of the trunk with lymphatic, capillary, venous and combined Vascular malformations, Epidermal naevi, Scoliosis/Skeletal and Spinal anomalies.

Epidemiology

It is unknown. This Syndrome is included in the ministerial list of rare diseases.

Etiology

CLOVES Syndrome belongs to the group of conditions called PROS, caused by activating, mosaic mutations in *PIK3CA* gene.[1]

Clinical aspects

Mosaic distribution of lesions and asymmetric overgrowth with skeletal anomalies. The Syndrome is characterized by an overgrowth of adipose tissue (lipomas), more frequently in the thorax and/or in the abdominal wall. Lipomas can extend to groin, retroperitoneum and mediastinum. The epidermal nevus is quite common. Abnormalities of the viscera and central nervous system can be associated. Patients with CLOVES Syndrome manifest a wide variety of vascular anomalies: more frequently low-flow anomalies (capillaries, venous and lymphatic) and less frequently high-flow anomalies (arteriovenous malformations in the paraspinal region or adjacent to the lipomatous masses). Lymphatic malformations can be microcystic, macrocystic or combined and frequently occur adjacent to the lipomatous masses of the trunk or abdomen.[2-4]

Other associated anomalies:[2-4]

- musculoskeletal (asymmetric overgrowth of the extremities [hands and feet] anomalies of the extremities: macrodactyly, polydactyly, sandal gap, syndactyly. Pectus excavatum and progressive scoliosis);
- visceral abnormalities (renal hypoplasia/agenesis, renal cysts, hydroureteronephrosis, Wilms tumor,[5] splenic lesions);
- neurological anomalies (spinal or paraspinal arteriovenous malformations; spina bifida, hypoplasia or agenesis of the corpus callosum, hemimegalencephaly, polymicrogyria, neuronal migration defects).

Diagnosis

Diagnosis is clinically performed and is confirmed by identification of PIK3CA gene mutation.[4]

Instrumental diagnostics uses the following imaging tests:[4]

- brain and medullary magnetic resonance imaging for the classification of cerebral and spinal anomalies;
- medullary MRI and angiography for the study of arteriovenous malformations;
- MRI, computed tomography, Doppler ultrasound for the classification and characterization of vascular malformations;
- abdominal ultrasound for the identification of visceral abnormalities.

Other clinical evaluations needed are:

- evaluation of clinical genetics for the genetic-molecular framework;
- evaluation of the vascular surgeon for the characterization of vascular malformations;
- orthopedic evaluation for the classification of musculoskeletal anomalies;
- dermatological evaluation for the identification of skin abnormalities;
- neurological/neuropsychiatric evaluation in case of psychomotor retardation and/or brain anomalies.

Treatment

The clinical complexity of CLOVES syndrome requires a multidisciplinary follow-up involving different specialists: vascular surgeon, pediatrician, orthopedist, plastic surgeon, neurologist/child neuropsychiatrist, dermatologist, nephrologist, neuroradiologist, neurosurgeon and other specialists according to clinical needs.

The treatments are conservative, rehabilitative and surgical. The surgical approach is intended for the removal of lipomas and lymphatic malformations (possible sclerotherapy of macrocystic forms), for the correction of hand and foot abnormalities, of lower limbs asymmetry and for the embolization of spinal AVMs.

Progressive scoliosis may require a surgical approach.[5]

Psychological support for the patient and family is indicated.

Off-label drug therapy with inhibitor of the PIK3-AKT-mTOR pathway (Sirolimus) is currently being tested.[6]

Hematological evaluation is indicated for the definition of thromboembolic risk.[7]

Question 1

Is there an increased prevalence of embryonic neoplasia such as Wilms' tumor in patients with CLOVES syndrome?

INTERPRETATION OF THE DATA

To answer Question 1, the research article[5] was analyzed.

The retrospective study conducted at the Children's Hospital of Boston on 122 patients with CLOVES syndrome showed an incidence of Wilms tumor (WT) equal to 3.3%, which is a higher incidence compared to general population (1/10,000; P<0.001). The authors recommend periodic (quarterly) ultrasound of the abdomen from birth up to 7 years of life (greater benefit under 3 years). This examination allows early identification and treatment of Wilms tumor without inducing adverse events. It is an acceptable instrumental examination for patients, as it is noninvasive, although family compliance is required due to the frequent intervals' execution during the first years of life.

Recommendations

In patients suffering from CLOVES syndrome, periodic abdominal ultrasound screening is indicated for the early identification of Wilms tumor from birth up to 7 years of life.

Strong recommendation in favor, level of evidence 3

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CLAPO

Definition

It is the acronym of Capillary Malformation of the Lower Lip, Lymphatic Malformation of the Face and Neck, Asymmetry and Partial/generalized Overgrowth.[1]

It is a condition of recent identification.

Epidemiology

Unknown.

Etiology

It belongs to the group of conditions called PROS, caused by activating mosaic mutations in *PIK3CA* gene.[2]

Clinical aspects

It is characterized by a capillary malformation limited to the lower lip associated with progressive hypertrophy of the

same lip (macrocheilia) in all patients and lymphatic malformations in the face or in the tongue. More rarely it affects the lower limbs. Venous malformations are quite common, even if they are not the main feature of the Syndrome. It is possible to observe an asymmetry and partial or total hypertrophy of a body segment unrelated to the vascular malformation. It is not associated with intellectual disability.[1, 2]

Diagnosis

Diagnosis is clinically performed and is confirmed by identification of *PIK3CA* gene mutation.[2]

Instrumental diagnostics used are magnetic resonance imaging, maxillofacial computed tomography and echo color Doppler for the identification and characterization of vascular malformations.

Evaluation of clinical genetics for the genetic-molecular framework is suggested.

Treatment

Treatment options are lip plasty and a surgical and/or sclerosing treatment of the lymphatic-venous component. Off-label drug therapy with inhibitor of the *PIK3-AKT-mTOR* pathway (Sirolimus) is currently being tested.[3]

The follow-up is carried out by a multidisciplinary team.

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FAVA

Definition

It is a complex vascular malformation (involving intramuscular and extra-fascial districts), which has been described for some years[1] and recently included in the group of vascular anomalies related to the somatic mutation of *PIK3CA* gene (PROS).[2]

Epidemiology

It is a rare condition, with a predominantly onset in adolescence and more common in females.

Etiopathogenesis

The somatic mutation of *PIK3CA* gene has been recognized as a mutation associated with FAVA.[2]

Clinical framework

FAVA most frequently affects the lower limbs, particularly the gastrocnemius muscle, but it can also affect the muscles of the feet, thighs and trunk. Skin involvement is absent or minimal.[3] A case series has recently been reported, with signs limited to upper limbs.[4] It can cause complex symptoms including persistent pain, malaise, functional impediment and contractures related to the presence of venous or venous/lymphatic vascular malformations, associated with hypertrophy of the intramuscular adipose and fibrous tissue, sometimes with foci of lympho-plasma cell infiltrate. When affected, the skin presents mainly venous and/or lymphatic malformations.[5]

Diagnosis

Although useful as a first approach examination, ultrasound has limitations in identifying complex vascular anomalies, while MRI is the most accurate diagnostic tool.[3, 6] Intralesional venography is performed during interventional procedures for sclerosing treatment.[5] In some cases, the differential diagnosis is posed with benign muscle tumors related to the *PTEN* mutation in Bannayan-Riley-Ruvalcaba Syndrome or Cowden Syndrome: in such cases, histological examination or needle biopsy may be indicated.[5]

Treatment

Conventional treatment includes a conservative, sclerosing, or surgical approach. Sclerotherapy is often the first therapeutic approach, but it frequently fails. Radical surgery can be decisive in a definitive way, but it is often excessively destructive.[6]

Percutaneous cryo-ablation represents a new, alternative, minimally invasive, therapeutic approach for the treatment of pain.[7]

Finally, systemic therapy with Sirolimus has recently been used successfully in isolated cases.[8]

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Diffused capillary malformation with overgrowth (DCMO)

Definition

The Diffuse Capillary Malformation with Overgrowth[1] syndrome is a condition of recent identification.

Epidemiology

Unknown.

Etiology

It belongs to the group of conditions called PROS, caused by activating, mosaic mutations in *PIK3CA* gene.[1]

Clinical aspects

DCMO is characterized by a diffuse and extensive reticular capillary malformation, associated with overgrowth of a limb or of the entire hemisome. Capillary malformations are most commonly localized in the trunk and in the extremities. Anomalies of the hands and feet (syndactyly, macrodactyly, sandal gap) may be present.[1, 2]

Diagnosis

Diagnosis is clinically performed and is confirmed by identification of *PIK3CA* gene mutation.[1]

Instrumental diagnostics uses Doppler ultrasound for the identification and characterization of vascular malformations.

Radiological evaluation of the lower limbs is needed, as well as a possible MRI to study the overgrowth localization.[2]

Evaluation of clinical genetics for the genetic-molecular framework is suggested.

Treatment

Conservative therapy is the first-choice treatment. A pulsed dye laser can be applied on capillary malformations. Orthopedic monitoring of leg length discrepancy is needed.[2]

These treatments include a multidisciplinary follow-up involving various specialists: pediatrician, vascular surgeon, orthopedist.

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Macrocephalia-capillary malformation (M-CAP)

Definition

M-CAP is the acronym of Megalencephaly- Capillary Malformation Syndrome.[1]

Epidemiology

Unknown.

Etiology

It belongs to the group of conditions called PROS, caused by activating mosaic mutations in *PIK3CA* gene.[1]

Clinical aspects

M-CAP is defined by three main characteristics:[1]

- congenital megalencephaly or hemimegaloencephaly associated with neurological symptoms (hypotonia, epilepsy, moderate/severe intellectual disability);
- skin capillary malformation, more frequently in the face, or widespread;
- segmental or generalized overgrowth.

Megalencephaly may be associated with malformation of the cerebral cortex (polymicrogyria), ventriculomegaly, ectopy of the cerebellar tonsils and thickening of the corpus callosum.

Finger anomalies (polydactyly, syndactyly) and connective tissue dysplasia (skin hyperelasticity, joint hyperlaxity, soft texture of the skin and subcutis) may also be present.

Overgrowth can involve the bone tissue of the lower limbs with consequent discrepancy.

A minority of patients have heart malformations.[1]

Diagnosis

Diagnosis is clinically performed, and it is confirmed by identification of *PIK3CA* gene mutation.[1]

Instrumental diagnostics uses brain and medullary magnetic resonance imaging and brain and craniofacial computed tomography for the classification of brain abnormalities.

Echo color Doppler can be helpful to identified and characterize vascular malformations.

Evaluation of clinical genetics for the genetic-molecular framework is suggested.

Orthopedic follow-up of somatic asymmetries is indicated. Cardiological screening by means of electrocardiogram and echo-cardio color Doppler for the search for associated cardiac malformations and periodic abdominal ultrasound screening for oncological risk are also indicated.[1]

Treatment

Conservative therapy.

The follow-up is multidisciplinary with the involvement of various specialists: vascular surgeon, pediatrician, child neurologist/neuropsychiatrist, neuroradiologist, orthopedist.

Neuroradiological follow-up is recommended every 6 months from birth to 2 years and annually from 2 to 6 years.[1]

In view of the lack of evidence, ultrasound screening is recommended for the early identification of the onset of Wilms tumor, similarly to CLOVES syndrome.[2]

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Parkes-Weber Syndrome (PKWS)

Definition

Parkes-Weber Syndrome (PKWS) is often misdiagnosed and confused with Klippel-Trenaunay Syndrome: according to many authors this condition is also referred to as Klippel-Trenaunay-Weber Syndrome.

Both Syndromes share the presence of a complex capillary-venous-lymphatic vascular malformation, associated with skeletal and soft tissue hypertrophy of a limb: in 87.5% of cases a lower limb up to the pelvis is involved, but also the upper limb can be affected.

Epidemiology

It is unknown; no gender prevalence was reported.

Etiology

It is related to a mosaic mutation of *RASA1* gene.[1, 2]

Diagnosis

The following diagnostic investigations[3] are fundamental for the diagnosis of PKWS: Color Doppler ultrasound,[4] MRI angiography and CT angiography for the detection of intralesional arteriovenous shunts.[5, 6]

To complete the diagnosis, the molecular-genetic test on biopsy of the tissue affected by the malformation is indicated to search for mosaic mutation of *RASA1* gene.

Selective arteriography is no longer performed for diagnostic purposes, but contemporarily with embolization procedures, because MRI and CT angiography methods provide sufficient information and have the advantage of not being as invasive as angiography.

Treatment

Therapeutic management is conditioned by the presence of arteriovenous malformations, and it includes a conservative approach (elastic compression, laser treatment of bleeding skin lesions), radiological interventions (embolization of artero-venous shunts by selective catheterization), surgery (phlebectomy, debulking of pathological tissue up to progressive limb amputation in extreme cases), orthopedic interventions to correct the dysmetria (epiphysiodesis).

The primary focus in the clinical management of PKWS patients should be improvement in quality of life and prevention of complications.

Indications for surgical treatment include recurrent venous ulcers and recurrent bleeding, chronic pain, presence of arterial aneurysms, distal arterial ischemia, secondary heart failure. The occlusion or surgical removal of the arteriovenous malformation by embolization possibly associated with surgical resection of the nidus/amputation lead to a clinical improvement with consequent improvement in the quality of life and a reduction in the risk of disease progression.

Question 1
What are the fundamental diagnostic investigations for the purposes of the differential diagnosis between KTS and Parkes-Weber Syndrome?

The presence of an arteriovenous malformation represents the distinguishing criterion between PKWS and KTS. The presence of arteriovenous shunts can determine serious long-term complications such as the onset of heart failure

(up to 31.3% of cases), distal venous hypertension, venolymphatic insufficiency, venous ulcers, peripheral hypoxia with distal skin necrosis, bleeding, chronic pain. The extension to the spine is exceptional, resulting in myelopathy.

The diagnostic investigations necessary for the detection of intralesional arteriovenous shunts are the following: Color Doppler, MRI/CT angiography.

To complete the diagnosis, the molecular-genetic test on a bioptic specimen affected by the malformation is indicated to search for mosaic mutation of the RASA1 gene.

INTERPRETATION OF THE DATA

To answer Question 1, 1 systematic review,[3] 2 narrative reviews[4, 6] and 2 case series[2, 5] were identified in the literature, describing patients with Parkes-Weber Syndrome and defining that presence of arteriovenous shunts in the context of vascular malformation is a pathognomonic feature for the purpose of the differential diagnosis with Klippel-Trenaunay Syndrome.

The conclusions of the analyzed studies are consistent with each other.

Experts agree that the presence of intralesional arteriovenous shunts negatively affects the prognosis and changes the patient's therapeutic path.

The damages deriving from an incorrect diagnostic classification of PWS would be greater than the costs deriving from the diagnostic investigations necessary for a correct classification.

The impact of instrumental radiological diagnostics is acceptable for patients and family members.

The necessary instrumental diagnostics should be performed in specialized reference structures for the treatment of Vascular Malformations.

The studies are relevant to the target population and argue about relevant comorbidities.

There are no concerns about possible bias.

Recommendations

For the purposes of diagnosing patients with PWS angioMRI and/or angioCT are recommended.

Strong recommendation in favor, level of evidence 2++/3

Question 2

Is invasive treatment with embolization and demolition surgery indicated in patients with PWS to improve the quality of life?

The primary goal in the clinical management of PKWS patients should be to improve the quality of life and contain complications.

Indications for surgical treatment include recurrent venous ulcers and recurrent bleeding, chronic pain, presence of arterial aneurysms, distal arterial ischemia, secondary heart failure. The occlusion or surgical removal of the arteriovenous malformation by embolization possibly associated with surgical resection of the nidus/amputation lead to a clinical improvement with consequent improvement in the quality of life and a reduction in the risk of disease progression.

INTERPRETATION OF THE DATA

To respond to KQ2, 1 systematic review[3] has been identified in the literature, which describes the diagnostic and therapeutic pathway of patients with Parkes-Weber Syndrome. The retrospective studies analyzed by the review agree in affirming the benefits of invasive treatment by means of embolization and/or surgical destruction of the arteriovenous nidus in patients with Parkes-Weber Syndrome, are relevant to the target population and argue about relevant comorbidities. The expected benefits from the treatment are represented by the improvement of the clinical picture, the quality of life of the patients and the reduction of complications related to the progression of the disease. The potential damages deriving from invasive treatment are represented by: incomplete occlusion of the arteriovenous nidus with recurrence of symptoms, pulmonary embolism, skin ulcers, surgical wound dehiscence. Invasive treatment requires hospitalization and sedation, surgical wound dressings and has a major impact on the patient, however after thorough counseling it is accepted by the patient and family members. Invasive treatment should be performed in specialized reference structures for the treatment of vascular malformations.

The possible biases highlighted by the review are the following: absence of randomized studies and short-term follow-up of the patients under examination, which could distort the results shown.

Recommendations

In order to improve the quality of life of PKWS patients with disabling symptoms, invasive treatment of arteriovenous malformation by embolization and demolition surgery could be indicated.

Weak recommendation in favor, level of evidence 2++

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Proteus syndrome (PS)

Definition

PS is an extremely rare condition characterized mainly by segmental (mosaic) overgrowth of various body tissues. The overgrowth is asymmetrical and progressive.[1, 2]

Epidemiology

Extremely rare (<1/1,000,000).

Etiology

PS is a sporadic genetic condition, caused by a pathogenetic variant (recurrent mutation), mosaic, in *AKT* gene (*c.49G>A; p.Glu17Lys*).[2]

Clinical aspects

Segmental and/or irregularly diffuse overgrowth, which can involve bone tissue, skin, adipose tissue and the central nervous system. Internal organs can also be affected by overgrowth. The spleen, kidneys, testes, tonsils and adenoids are most frequently involved. Congenital onset of hemimegaloencephaly with possible consequent neurological involvement and cognitive deficit. The overgrowth of bone and soft tissue occurs in particular at the level of the limbs during early childhood (6-18 months), with progressive aggravation to the point of causing disfiguring and disabling deformities.

Dermatological anomalies may be present, such as the cerebriform nevus, which is mainly localized on the soles of the feet, hands, face. It is rare that it is congenital, it becomes evident during childhood with progression during adolescence.

Abnormalities of adipose tissue include regional overgrowth of adipose tissue associated or not with regional lipoatrophy.

Vascular malformations more frequently are capillary, venous and lymphatic malformations. Arteriovenous malformations are rare.

Bullous lung disease is rather unusual, although it has been identified in some patients with PS in late childhood or adolescence.

Minor facial abnormalities include dolichocephaly, elongated face, downward-turned eyelids, depressed nasal root, anteverted nostrils.

PS patients also show predisposition to the development of tumors at a young age (many of them benign): meningioma, ovarian cystadenoma, parotid adenoma, testicular neoplasia.[1-3]

Diagnosis

The clinical diagnosis of Proteus Syndrome is based on the presence of the following general and specific criteria.[2, 4]

General criteria were:

- mosaic distribution of the lesions;
- sporadic case;
- progressive course.

Specific criteria are listed below.

- A category (cerebriform connective tissue [cerebriform nevus]);
- B category:
- linear epidermal nevus;
- asymmetrical and progressive hypergrowth;
- onset within the second decade of the following neoplasms: bilateral ovarian cystadenoma, parotid adenoma;
- C category:
- adipose tissue growth dysregulation (lipoma, regional lipoatrophy);
- vascular malformation: capillary, venous, lymphatic;
- bullous lung degeneration;
- facial abnormalities (dolichocephaly, down slanting eyelid rims, sunken nasal root, anteverted nostrils).

For the clinical diagnosis of Proteus Syndrome, all general criteria are needed in association with:

- the category A criteria or;
- two criteria belonging to category B, or;
- three criteria belonging to category C.

If the clinical criteria are inconclusive, the identification of the mosaic pathogenetic variant in *AKT1* gene allows to perform the diagnosis of Proteus Syndrome.

The tests aimed at the diagnosis are: MRI of the affected body regions; chest and abdomen MRI even in the absence of symptoms; radiological evaluation of the skeleton; possible computed tomography in the presence of scoliosis; oncological evaluation.[3]

Evaluation of clinical genetics for the genetic-molecular framework is suggested.

At the time of diagnosis, it is also indicated to perform:

- a screening abdomen ultrasound;
- a lung evaluation in subjects with signs or symptoms of bullous lung disease;
- a neuropsychiatric evaluation in subjects with delayed psychomotor development.[3]

Treatment

The therapy is conservative and rehabilitative. Pharmacogenetic therapies (*AKT1* inhibitor) are being studied.[5,6] The clinical complexity of the PROTEUS Syndrome requires a multidisciplinary follow-up involving several specialists: vascular surgeon, dermatologist, orthopedist, hematologist, child neurologist/neuropsychiatrist, oncologist, radiologist. Other specialists might be contacted according to clinical needs.

On the basis of clinical data, it is indicated to perform:

- clinical surveillance of cancer risks every 6-12 months;[3]
- orthopedic monitoring;[7]
- periodic abdominal ultrasound monitoring in patients with focal hepatic or splenic lesions;[3]
- periodic echo color Doppler monitoring of splanchnic vessels in patients with thrombocytopenia and splenomegaly to check for possible development of portal hypertension or portal vein thrombosis;[8]
- hematological evaluation to ascertain or exclude the thrombo-embolic risk;[5, 10]
- in consideration of the severity of the condition, psychological support for the patient and family is indicated.

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Distinctive criteria: clinical, epidemiological and therapeutic criteria of group B syndromes

Sturge-Weber Syndrome (SSW)

Definition

Sturge-Weber Syndrome (SWS) is characterized by a capillary malformation of the face associated with a vascular anomaly of the leptomeninges and with glaucoma. Not all three manifestations are needed to define the disease. In fact, three forms of SWS are distinguished: type I (characterized by the characteristic triad), type II (cutaneous and ocular manifestations) and type III or incomplete type (characterized only by cerebral involvement).

Epidemiology

According to the American National authority for rare diseases, Sturge Weber Syndrome has an incidence of 1/20,000-50,000 live births. It is a sporadic condition with no difference in incidence in the territory.[1]

Etiopathogenesis

It is caused by a somatic mutation (gain of function) of *GNAQ* (p.R183q) and *GNA11*[2, 3] genes. The dermis of the face is composed of cells originating from the forebrain. A very early mutation of one of these two genes in the forebrain causes abnormal vascularization of the skin of the frontal-eyelid region and a possible vascular malformation in the ocular and in the pia mater.

In the paper by Shirley *et al.* Missense variants have been identified in *GNAQ* gene in tissue originating from 88% of patients with SWS and in none of the tissues from healthy or other patients [2]. In the study by Polibothu *et al.* one patient with SW was affected by a mosaic mutation in *GNA11* gene. This patient presented with extensive cross-linked capillary malformation including the forehead, glaucoma and hypotrophy of the right side of the face and right leg.[3]

Clinical aspects

The presence of a cutaneous capillary malformation extended to the upper quadrants of the head may represent a symptom of a Sturge-Weber syndrome (SWS), in which leptomeningeal and ocular involvement is observed. The involvement of the frontal-eyelid area, with lateralized mono- or bilateral distribution and with possible extension to the frontal-parieto-temporal scalp and/or to the lower segments of the face is predictive for SWS.[4, 5]

Seizures are common and often severe. They are present in 75% of unilateral cases and in 90% of bilateral cases. The early onset of epilepsy, the high frequency of seizures and bilateral involvement are negative prognostic signs from a cognitive point of view.[6]

In addition to epilepsy, the syndrome can lead to other neurological problems such as migraines, hemiparesis, developmental delay/intellectual disability and cerebral ischemic-like episodes. The latter are characterized by sudden onset of motor disturbances (*e.g.*: hemiparesis) and visual disturbances that are difficult to distinguish from acute epileptic seizures, lasting hours or days. These symptoms would be determined by cortical ischemia induced by the cerebral vascular malformation. Thrombotic episodes would be at the basis of these phenomena and for this reason a prophylactic treatment with acetylsalicylic acid at a dose of 3-5 mg/kg/day has been proposed to prevent neurological worsening of these patients.[7] However, there is a lack of randomized clinical trials to support this treatment. Side effects of low-dose aspirin therapy are generally mild and mostly attributable to post-traumatic bruising, epistaxis, and gingival bleeding.

Headache is present in 30-45% of cases[8] and it has a significant impact on patients' quality of life. Migraine with prolonged aura associated with hemiplegic attacks is frequent. These symptoms lead to cognitive, behavioral and learning problems that affect mood in a negative sense due to the onset of depressive and/or anxious neurosis. While epilepsy is typical of the first years of life, headache generally occurs in school age along with behavioral problems. Depression and psychiatric disorders in general characterize adolescence and adulthood.

Patients with SWS often have adaptation as well as cognitive disorders. While the latter would be related to the frequency and intensity of epileptic attacks, adaptation disorders correlate with the presence and severity of paretic and above all paralytic phenomena.

Sixty percent of SWS patients have mental retardation,[9] which is severe in 33% of cases. ADHD affects 40% of patients.[10] The use of stimulants for the treatment of ADHD would have shown subjective benefits without significant side effects.

Behavioral problems are typical of adolescents and adults and certainly find at least part of the premises in the presence of the capillary malformation of the face and in the aforementioned neurological and cognitive problems. The capillary malformation is also very often associated with hypertrophy of the underlying soft tissues, with asymmetry of the face and often involvement of the dental arches and gingival mucosa with possible dental complications. Most patients experience anxiety and depression, feelings of shame and isolation.[11] The quality of life of these patients is at least partially compromised by the presence of the vascular stain on the face which makes them socially recognizable.[12] Also, for this reason, laser treatment of the capillary malformations of these patients is important. According to some studies, the exposure of pediatric patients to repeated anesthesia for laser treatment would not increase the risk of neurodevelopmental disorders compared to the population.[13] In other papers, however, the conclusions are different and there are suspicions for a reduction in neurological development in patients undergoing repeated narcosis (≥3) at the age of less than 4 years.

When the eye is affected in SW syndrome, episcleral and choroidal vascular anomalies and heterochromia of the iris can be observed. Glaucoma is the most frequent complication with possible damage to the optic nerve due to increased intraocular pressure.[14] Sixty percent of patients develop glaucoma in childhood and the remainder develops it in pediatric or adulthood.

It is thought that glaucoma can be generated by the vascular malformation of the anterior chamber and by the increased pressure of the episcleral vein.

Diagnosis

The eye examination is indicated for all newborns with a high-risk capillary malformation of the frontal-nasal region. This must be done as soon as possible to diagnose any glaucoma by measuring eye tone (tonometry). Given the risk of developing glaucoma even beyond childhood, periodic checks are required with or without sedation of the patient based on the patient's cooperation. Since the risk of developing glaucoma persists for life in these patients, an annual eye checkup in adults would also be recommended.

Electroencephalogram (EEG) is an extremely useful exam in patients with SWS. In particular, the presence of EEG alterations could predict the onset of seizures and the

identification of intercritical Spikes would have a positive predictive value for the development of cognitive deficits.

Brain magnetic resonance imaging is the fundamental examination for confirming neurological involvement. Especially in patients younger than 2 years of age, it should be performed with specific sequences and interpreted by an experienced radiologist. In fact, in the first year of life, false positives secondary to incomplete cerebral myelination are possible. In this period, the MRI investigation is indicated only in the case of neurological symptoms. A study without sedation and contrast medium can avoid the risks associated with the deposition of gadolinium in the tissues and provide information on cortical venous anomalies, meningeal, choroidal plexus or on the presence of engorgement of medullary and ependymal veins, encephalomalacia, atrophy and calcifications. [15] In any case, in the asymptomatic patient, the complete study with the contrast medium could be indicated after the completion of the first year of age, as suggested by an American multidisciplinary consensus. [16]

In patients with neurological symptoms, MRI with contrast medium under sedation is indicated. In the event of a negative test, in children under 2 years of age it will be advisable to repeat the same after 1-2 years.

In some recent studies, the possibility of obtaining information equivalent or superior to MRI with gadolinium has been identified through the quantitative analysis of the ADC (Apparent Diffusion of Contrast). [6]

In stable patients it is not necessary to repeat the MRI routinely, but only in case of symptoms worsening.

Many authors underline the importance of early electroencephalographic and neuroradiological evaluation even in asymptomatic patients due to intracranial involvement in order to recognize patients at risk of developing neurological problems. However the sensitivity, specificity and predictive values of these investigations, in the absence of specific pharmacological treatment or surgical procedures, are still controversial.

To complete the diagnosis, genetic counseling and molecular-genetic examination on biopsy sampling of the tissue affected by the capillary malformation may be indicated for the search for somatic mutation in *GNAQ* (p.R183q) and *GNA11* genes.

Treatment

The control of epileptic seizures is fundamental for the patient's prognosis from a cognitive point of view. It is important to warn the family in advance of the risk of epileptic seizures in patients with SW syndrome to organize themselves for any emergency with the administration of benzodiazepines. Families should also be educated on the signs of possible seizures in younger children where they may be mistaken for small behavioral abnormalities. Parents should take note of any changes in the child's attitudes and behaviors and report them to the specialist. In case of altered mental status, an electroencephalogram is also suggested to exclude the possibility of a non-convulsive epileptic status.

There are no guidelines for the management of headache in SW patients. Sleep, ibuprofen, patient hydration and the use of antiemetics are suggested.

Prophylaxis of seizures with antiepileptic drugs such as Valproic Acid, Levetiracetam, Tegretol And Topiramate Has been proposed, but there are concerns about the latter regarding a possible worsening of glaucoma. However, the pathophysiology of glaucoma development in SWS patients is different and in the studies that evaluated it, topiramate was not associated with an increased risk of developing glaucoma. This should be borne in mind especially for the use of topiramate as an additional drug in epileptic seizures unresponsive to monotherapy and possibly as anti-migraine prophylaxis. The use of antiepileptic therapy before the onset of seizures has been evaluated in individual reports, however it is considered by most clinicians as very controversial and contraindicated.

Other hygienic devices strongly recommended for the prevention of crises / headache / stroke-like events are a balanced diet, a regular sleep/wake rhythm, adequate hydration during intercurrent infectious events and the prevention of head trauma, saving the patient from sporting or recreational activities at risk.

In subjects at risk for known intracranial involvement, the neurologist/neuropsychiatrist specialist will evaluate whether to start neuropsychiatric tests from the age of 3-4 to diagnose patients at risk early and implement the appropriate educational and behavioral interventions.

Patients with epileptic episodes refractory to medical therapy and especially those with unilateral leptomeningeal capillary malformation can undergo neurosurgical treatment with a significant reduction in the frequency and intensity of seizures. Surgery often leads to their permanent resolution. The type of surgical treatment must necessarily be evaluated in a Specialized Epilepsy Surgery Center.

Photocoagulation using pulsed Dye-laser is the first-choice method for the treatment of capillary malformation of the face and to improve the psychological conditions of the patient related to the aesthetic appearance. The effectiveness of the treatment is greater if performed

in early childhood. Other therapeutic options are also possible such as the association with topical Rapamycin or the use of sequential laser technologies that provide for the delivery in rapid sequence of a double Dye-Nd: YAG pulse: the two pulses at different wavelengths (respectively 595-1064 nm) emitted at a distance of a fraction of a second allow the preliminary transformation of oxyhemoglobin into methemoglobin and a subsequent penetration of the Nd: YAG radiation up to a depth of 7-8 mm. The sequential method is indicated for the treatment of hypertrophic capillary malformations or those resistant to treatment with laser dye.[17,18] In view of the controversies in the literature about the repeated use of anesthesia for the treatment with Dye laser and the effectiveness of different lasers, it is advisable to have adequate informed consent with the patients' families, informing the parents of all the therapeutic possibilities and current knowledge.

At the moment, the first-choice treatment of SW-related glaucoma is topical therapy with beta-blockers, that reduce the production of aqueous humor, prostaglandins, that increase the outflow of aqueous humor, and alpha-agonists, that act on both factors. Goniotomy and trabeculotomy surgery are the surgical treatments of first choice, complications are more frequent in these patients and success is reduced compared to the population without SW.[19] Surgical correction of the hypertrophy of soft and skeletal tissues of the face can improve the symmetry and harmony of the face 2[0] with obvious psycho-social benefit.

Question 1

In the presence of a capillary malformation of the face involving the skin of the forehead with a distribution suggestive of Sturge Weber Syndrome, in the absence of neurological symptoms is it indicated to perform a neurological examination with EEG for the purpose of early diagnosis of neurological problems?

INTERPRETATION OF THE DATA

The answer to question 1 is based on the results presented by the study by Bar *et al.*, 2018.[21] 11 patients were examined. In 8 of these there were asymmetries in the EEG tracings and in 5 there were no asymmetries. Of these 8 patients, 6 subsequently developed seizures. The presence of Spike or "Sharp Waves" was then evaluated in the EEGs. These were present in 6 patients. Five of these subsequently developed seizures. Of the patients who did not have EEG abnormalities, one developed epileptic seizure. The study suggests good positive and negative predictive value. However, this is a case-series on only 11 patients and therefore the scientific validity is unfortunately limited.

Recommendations

In the presence of a capillary malformation of the face involving the skin of the forehead with a distribution suggestive of Sturge Weber Syndrome, even in the absence of neurological symptoms it is indicated to perform a neurological examination with EEG for the purpose of early diagnosis of neurological problems potentially related to the Sturge Weber Syndrome.

This diagnostic investigation is not indicated for congenital midline capillary macules with frontal-eyelid extension that present spontaneous resolution, defined as "nevus flammeus neonatorum".

Strong recommendation in favor, level of evidence 3

Question 2

In patients with capillary malformations of the face, early treatment in pediatric age by means of pulsed laser dye photocoagulation is indicated to improve the patient's psychological conditions.

In patients suffering from Sturge Weber Syndrome with capillary malformation of the face, is the association with topical antiangiogenic drugs (Rapamycin) indicated compared to Pulse Dye-laser treatment alone?

In patients suffering from capillary malformation of the face, early treatment in pediatric age by photocoagulation with pulsed laser dye is indicated to improve the psychological conditions of the patient related to aesthetic appearance (see therapeutic recommendations in the Chapter on Capillary Malformations).

INTERPRETATION OF THE DATA

To answer question 2, a phase II randomized double-blind placebo/control study was analyzed: Marques L 2015.[21]

The study is based on 23 patients with SW on whom 4 interventions were evaluated: placebo, PDL, rapamycin, and PDL + rapamycin. The clinical and histological response was evaluated at various intervals after surgery.

The population is very limited (23 patients); the methodological quality seems good but, given the limited sample size, it cannot provide robust indications regarding efficacy and safety. The study is consistent with the conclusion even though statistical significance limits the strength of the recommendation. The study includes a target population and makes a direct comparison. The ben-

efits are likely, since the association with rapamycin gave the best score and the maximum reduction of capillaries to histology compared to other interventions. The damage could result from an absorption of rapamycin through the affected skin. Feasibility is an issue because topical rapamycin treatment is off-label and expensive and not guaranteed by the national health system. For this reason it would be totally borne by the patient. Although the study is well constructed in favor of the use of rapamycin, the small number of patients invalidates the statistical significance and the difficult feasibility (off-label use) limits its possible application.

Recommendations

According to some authors, the association of the Dye Laser treatment with antiangiogenic drugs for topical use (Rapamycin) could be indicated in SWS patients, but the application on the Italian territory is difficult to achieve as the treatment is off-label.

Recommendation for research and for limited use in clinical trials

Question 3

In the presence of a capillary malformation that affects the eyelids, is it advisable to perform an eye examination quickly for the purpose of an early diagnosis of a possible glaucoma?

INTERPRETATION OF THE DATA

To answer question 3, a systematic review of the literature was analyzed.[22]

In the systematic review by Javaid *et al.*, it is confirmed that the involvement of the upper eyelid is a risk factor for glaucoma. The recommendation is based on a review proposal where the authors recommend as an expert opinion to prolong the patient's follow-up for life (Silverstein *et al.*). In Reyes-Capo's article on a series of patients the interested eyelid is identified as a risk factor for glaucoma. This recommendation can only lead to benefits deriving from the early diagnosis of glaucoma in the absence of possible damage. It will then be the ophthalmologist himself who decides whether the patient should undergo a visit in narcosis with ocular tone measurement. The studies cited are consistent with the conclusions.

The potential impact is positive because the early identification of patients suffering from glaucoma allows the most appropriate therapy to be rapidly established in order to avoid possible complications.

The intervention is easily implemented as it only requires the presence of an ophthalmologist inside the structure.

The recommendation is strong in favor since the benefits are certain. The delay in diagnosing a glaucoma, in fact, can lead to permanent and serious consequences.

Recommendations

In all newborns with a capillary malformation of the face that also affects the eyelid region, it is indicated to carry out an eye examination quickly for an early diagnosis of a possible glaucoma by means of tonometry.

This diagnostic investigation is not indicated for congenital midline capillary macules with fronto-eyelid extension that present spontaneous resolution, defined as "nevus flammeus neonatorum".

Strong recommendation in favor, level of evidence 2+

Question 4

In the presence of a capillary malformation of the face involving the skin of the forehead with a distribution suggestive of Sturge Weber Syndrome and in the absence of neurological symptoms, is it indicated to perform a brain MRI examination in the first year of life for the purpose of diagnosing a possible CNS involvement or is neuroimaging only indicated if neurological symptoms occur?

INTERPRETATION OF THE DATA

Carrying out the clinical evaluation alone (associated with EEG) is sufficient in the case of an asymptomatic child. Furthermore, MRI can be poorly reliable before the year of life due to technical and pathophysiological reasons, especially if performed without contrast medium, without ad hoc sequences and in non-specialized centers. The evidence is drawn from assessments expressed on the basis of expert opinion[24, 25] and from case series[21] and since there are no specific treatments available in children with intracranial involvement, the scientific evidence is very modest. The recommendation is strongly in favor since there are no clear advantages in performing an MRI before the age of one while the disadvantages are not negligible due to the need to perform deep sedation.

Recommendations

During the first year of life, in the presence of a capillary malformation of the face involving the skin of the forehead with a distribution suggestive of Sturge Weber Syndrome, neuroimaging by means of MRI brain examination with contrast medium is indicated only in case of neurological symptoms.

Strong recommendation in favor, level of evidence 4

In the presence of a capillary malformation of the face in-

volving the skin of the forehead with a distribution suggestive of Sturge Weber Syndrome, a neonatal screening by basal brain MRI examination may be indicated, performed in natural sleep without contrast medium in the first two months of life, while taking into account the low sensitivity and the high percentage of false negatives.
Recommendation based on good clinical practice, GPP

Question 5
Is drug therapy with acetyl-salicylic acid indicated for the prevention of progressive neurological deterioration over time in Sturge Weber Syndrome?

INTERPRETATION OF THE DATA

The analysis of the literature in this regard has produced exclusively articles based on expert opinion.[24, 25]

The administration of low-dose aspirin could reduce the risk of neurological insults due to the lack of thrombotic phenomena in the malformed vessels of the brain affected by the disease.

The side effects deriving from the administration of aspirin would be minimal and always controllable. However, it should be noted that the indication is still being discussed and there are some centers that do not place it.

The resulting recommendation is consequently strong in favor but the scientific evidence is scarce.

Recommendations
In Sturge Weber Syndrome there is no targeted drug therapy to contain the progression of neurological symptoms in the child. Pharmacological therapy with low-dose acetyl-salicylic acid (3-5mg / kg of weight) may be indicated for the prevention of progressive neurological deterioration over time.
Weak recommendation in favor, level of evidence 4

Question 6
Can surgical correction of soft tissue hypertrophy and skeletal deformities in Sturge Weber syndrome improve the symmetry and harmony of the face?

INTERPRETATION OF THE DATA

To answer question 6, a series of cases was analyzed.[23]

The article reports an interesting technique in two steps after months between the two phases. According to this approach, the dento-skeletal deformity is corrected in the first step and the soft tissue asymmetry in the second step.

Unfortunately, the extremely small number of cases (only 2 cases) prevents any consideration from being made on the applicability in the population of patients affected by SWS.

The results obtained are fair but the approach is intellectually valid. Therefore, the study is not very relevant and lacking due to the absence of comparators. However, the skeletal and soft tissue correction procedure in SWS-associated hypertrophy could produce a significant improvement in the facial symmetry of patients with evident psychosocial benefit.

The possible damages are related to the operative risk and possible complications of the intervention.

Overall, the intervention is likely to be beneficial and feasible in expert centers that manage vascular anomalies and have plastic or maxillofacial surgeons with experience in this field.

The desired effects probably outweigh the unwanted effects. Although there is no control population, the discomfort of the deformity of the face is known in this group of patients and the possibility of correcting or improving the deformity can be an undoubted advantage.

Recommendations
Surgical correction of the hypertrophy of the soft and skeletal tissues of the face could be indicated to improve the symmetry and harmony of the face.
Weak recommendation in favor, level of evidence 3

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Osler-Weber-Rendu Syndrome or hereditary hemorragic teleangectasia (HHT)

Definition

Hereditary hemorrhagic telangiectasia (HHT), also known as Rendu-Osler-Weber disease, is an autosomal dominant disease characterized by the presence of mucocutaneous telangiectasias and multiple district arteriovenous malformations. It is characterized by recurrent bleeding (epistaxis), multiple telangiectasias and arteriovenous malformations in major organs.[1, 2] The systemic presentation requires a multidisciplinary competence and the otolaryngologist plays a fundamental role in early diagnosis and treatment of Rendu-Osler-Weber disease, since one of the earliest and most obvious manifestations of the disease is epistaxis.

Epidemiology

Hereditary hemorrhagic telangiectasia is a rare disease, the incidence of which is difficult to calculate precisely due to a large number of undiagnosed cases. The prevalence of the disease is 1 in 5,000-8,000 people with equal distribution between the two sexes.[3] Mutations in *ENG* (HHT1) or *ACVRL1* (HHT2) genes were found in 85% of cases of patients with a confirmed diagnosis. In a minority of cases (1-2%), *SMAD4* mutations (which in 25% of cases arise de novo) associated with a high risk of developing intestinal polyposis or colorectal cancer have been identified.[4] More recent studies also identified the GDF2 gene as responsible for the disease (<1% of cases). In the remaining percentage (10-15%) the mutation is not detected, although the diagnosis can be confirmed according to clinical criteria.

Etiopathogenesis

Abnormally expressed proteins constitute receptors and co-receptors of the *TGFβ* protein expressed in endothelial cells.[3] The most accredited theory from recent studies states that the deficiency of proteins that mediate *TGFβ* signal transduction in endothelial cells is the cause of vascular abnormalities. It is not yet clear what is the exact mechanism that correlates genetic alterations to vascular structural defects, but, according to studies on mouse models, it is suspected that the single genetic alteration is not sufficient for the development of vascular alterations, and that an additional secondary proangiogenic trigger is necessary (*e.g.* ectopic expression of endothelial growth factor, inflammation, environmental factors, stress mechanical).[3]

Telangiectatic lesions present as a focal dilation of the post capillary venule which widens to connect with an arteriole which is in turn dilated. The result is an arteriovenous connection not intercalated by a capillary bed, associated with a perivascular lymphocyte infiltrate. AVMs are theorized to be the result of progressive vascular remodeling of these smaller lesions.[4, 5]

Clinical aspects

Manifestations in individual patients vary by age of symptom onset, frequency and severity of vascular lesions even within the same genetic subtype and the same family.[5]

The disease manifests itself with cutaneous and mucosal telangiectasias, mainly involving the nasal mucosa, skin, oral cavity and gastrointestinal tract, and arteriovenous malformations (AVMs) localized in the lung, liver and brain (more rarely they also affect the pancreas and the vessels of the spinal cord).

The most characteristic manifestations are epistaxis (95% of cases), mucocutaneous telangiectasias (80% cases) more evident in the lips, tongue, oral cavity, malar region and fingers.

The presence of visceral arteriovenous malformations can cause complications due to the presence of shunts or possible bleeding caused by the combination of fragility of the vessel and inadequate structure and high blood flow pressure.[5]

Epistaxis is a consequence of the presence of mucous telangiectasias in the nasal mucosa whose typically fragile walls break easily in the face of minimal thermal or mechanical insults. Some patients have infrequent and minor nosebleeds, while others may manifest serious pictures that cause profound anemia, significantly affecting the patient's quality of life.[6] Spontaneous and recurrent epistaxis are of variable magnitude and frequency and occur on average around 12 years of age or in any case prior to 21 years of age in almost all cases.[7]

Pulmonary AVMs are asymptomatic in most cases, but can complicate dyspnoic and hypoxemic pictures caused by arteriovenous shunts (complications that can occur especially after the fourth decade). The presence of shunts allows the occurrence of paradoxical embolisms of various kinds (bacterial, gas, from a deep vein thrombosis, etc.) which can determine pictures of ischemia or brain abscesses.[8]

Gastrointestinal AVMs (15-30%) can cause chronic oozing and consequent anemia and can be investigated by gastroduodenoscopy, video capsule and colonoscopy.[5, 9]

Hepatic AVMs are asymptomatic or show only a slight increase in GGT in 90% of cases. More rarely, an arterioportal shunt can cause complications such as portal hypertension, porto-pulmonary hypertension,[10] ascites, encephalopathy and hematemesis[10] or complications such as heart failure and necrotizing cholangitis due to theft of the arterial supply.[11] The ideal method for observing hepatic AVMs is Doppler ultrasound.

Cerebral vascular malformations (10-20%, most common in HHT1) in most cases present as arteriovenous fistulas and can cause cerebral hemorrhages, migraines, strokes, transient ischemic attacks and epileptic pictures. It is thought that these lesions are present from birth and that their development is completed during childhood.[5]

Spinal AVMs are significantly less frequent (<1% of cases) than brain AVMs and typically arise as paralysis or back pain.[6]

Diagnosis

To confirm the diagnosis of hereditary hemorrhagic telangiectasia, Curaçao criteria are used which include: recurrent spontaneous epistaxis, presence of mucocutaneous telangiectasia, presence of visceral arteriovenous malformations, positive family history for the disease.[5]

Diagnosis is confirmed with the presence of at least three of the criteria listed above.[4] With the presence of two of the four criteria, the disease is suspected while the presence of less than two criteria allows the diagnosis of HHT to be considered unlikely.[12] Diagnosis can be confirmed even in the absence of the Curaçao criteria by making use of the positivity of the genetic investigation.[13]

Applying diagnostic criteria to pediatric patients can be misleading, as symptoms and signs of the disease generally develop during adolescence and may be absent in children.[7] When the diagnosis is made, a genetic investigation is performed to identify the mutated gene. The research is also extended to the patient's family members as a screening aimed at identifying asymptomatic or poorly symptomatic cases.[5] The genetic defect is identified in 80-85% of cases.

Following the diagnostic confirmation and/or identification of the mutation, it is advisable to perform some clinical and instrumental investigations aimed at searching for any arteriovenous malformations. The complete physical examination with particular attention to the inspection of telangiectasias is essential for a correct clinical classification of the patient. The complete blood count must be repeated frequently in patients with recurrent bleeding. Bubble echocardium and chest CT are tests aimed at looking for any pulmonary shunts and AVMs or to identify early pulmonary hypertension. If the tests are negative, they will be repeated after 5 years. In the presence of a positive response, each case is entrusted to multidisciplinary evaluation to establish a therapeutic indication or to initiate the patient to follow-up with the aim of monitoring lesions that over time can reach such dimensions as to deserve treatment. For patients with small untreated AVMs or dubious or microscopic lesions, the follow-up period should

be determined on a case-by-case basis (between one and five years). The chest CT scan should therefore be performed within 6-12 months after embolization and then about every 3 years also to identify the possible reperfusion of injuries already treated.[14]

Liver ultrasound is a non-invasive and free of complications' procedure and is the examination of choice for the identification of hepatic AVMs, for diagnostic, therapeutic and prognostic purposes. Angiography, performed by catheterization, has traditionally been considered the diagnostic "gold standard," but it is an invasive test, and therefore more rarely used. The CT or MRI of the abdomen, although characterized by specific diagnostic accuracy, has a poor applicability due to the high costs, exposure to ionizing radiation and the secondary effects secondary to the administration of contrast medium.[14] Gastroscopy/colonoscopy are indicated in cases of chronic anemia not related to epistaxis or in the presence of melaena or hematemesis. It is recommended to perform a brain MRI at least once in life, preferably as early as possible, to be repeated for surveillance in case of positivity.[7]

Screening

Family members of patients diagnosed with HHT should be screened to identify potential undisclosed affects. Pulmonary screening is strongly recommended for all patients with possible HHT and is performed with a contrast echocardiography (Eco Bubble) or with a lung CT scan. Liver screening is generally performed through an abdominal Doppler ultrasound. In patients with a mutation of SMAD4 gene, screening also includes performing a colonoscopy from the age of 15.[14]

Prognosis

Most HHT patients who have access to health care have a life expectancy comparable to the general population. There was an increase in mortality in patients with presentation during childhood and adolescence, especially due to cerebral AVMs and, later on, complications that occurred during pregnancy.

Treatment

Since a therapeutic target has not yet been identified that allows the disease to be cured in a definitive way, the therapeutic approach includes a strategy of support and prevention of complications. Treatment must be personalized on the basis of the manifestations presented by the individual patient. One of the main therapeutic objectives is the control of epistaxis and iron deficiency anemia caused by recurrent bleeding. Chronic oozing anemia can be treated with iron orally or intravenously, or with the use of transfusions in severe cases.

The management of nosebleeds starts with the patient's correct information on home management, recommending the use of nasal ointments, humidification of the home environment and closing the nasal vestibule with greasy gauze. If such remedies are ineffective, both medical and surgical treatments may be considered.

Topical therapies are used to treat mild nosebleeds. The drugs that can be used for this purpose are tranexamic acid in gel, estrogen in ointment, topical mupirocin and topical bevacizumab. These are formulations that can be directly applied to the nasal mucosa, which represent a non-invasive option with no side effects due to the local absorption of the active ingredient. The disadvantage of this therapeutic strategy is represented by the poor applicability on cases of major epistaxis and by the subjective variability of the response to treatment. Some authors have also proposed the local injection of sclerosing substances with encouraging results, albeit performed on small series.[15]

Among the surgical options, as the first choice, endoscopic and minimally invasive treatments are preferable with the aid of delicate instruments (Argon-Plasma or laser) which allow the selective treatment of nasal telangiectasias, resulting well tolerated and repeatable.[16, 17] Embolization under angiographic control of the main arterial vascular supplies of the nasal cavities, it is a treatment with short-term efficacy, to be reserved for selected cases, as this too is not free from complications, even serious ones. The septodermoplasty operation, one of the first proposed interventions, today finds limited indications, acting only on lesions localized at the level of the nasal septum.

In refractory cases, with important impairment of the quality of life, surgical closure of the nasal cavities may be proposed. This irreversible method must be taken into consideration in case of failure to respond to all other less invasive treatments.[18]

Systemic therapies involve the use of drugs which, due to their formulation, can cause a series of side effects. On the medical side, new and recent lines of research have developed therapies directed against factors involved in the pathogenetic mechanisms of HHT. Oral thalidomide, for example, has shown efficacy in the control of nosebleeds with few side effects.[19-21] Bevacizumab, a monoclonal antibody directed against VEGF, was administered both intravenously and intranasally via submucosal or spray injections, with difficulty in finding a balance between efficacy and side effects.[5, 21] Pazopanib is a VEGF

inhibitor and is currently in a phase II clinical trial (placebo control).

Hormonal therapy was also proposed, with estrogen-progesterone and tamoxifen, based on observations regarding the ability of estrogens to induce squamous metaplasia on the respiratory epithelium, providing greater protection of the underlying telangiectasias.[7, 22] Other medical strategies have been put in place to intervene on the control of antifibrinolytic activity such as aminocaproic acid, with poor results, and tranexamic acid which instead showed a satisfactory efficacy in a certain percentage of cases.[7]

Bleeding oral telangiectasias can be treated with the aid of laser photocoagulation in multiple sessions.[17]

Embolization is the treatment of choice for pulmonary AVMs in adults and children and allows long-term benefits to be obtained, if performed in referral centers for the disease. The selection of cases to be treated by embolization is based on the diameter of the afferent arteriole, generally equal to or greater than 3 mm,[14] Patients with even asymptomatic pulmonary AVMs are precluded from diving and antibiotic prophylaxis is strongly recommended before undergoing surgery surgical or dental treatment.[7, 14]

Treatment of gastrointestinal AVMs is generally not necessary unless there is a failure of iron replacement therapy in order to maintain adequate hemoglobin level. Gastrointestinal lesions can be treated locally with endoscopic treatment.[7]

The treatment of cerebral AVMs when indicated uses techniques such as embolization, microsurgery and interventional radiology.[5]

Clinical questions, interpretation of the evidence and recommendations

The panel of authors formulated 5 clinical questions related to HHT disease. To answer these questions, the recent Second International Guidelines for the diagnosis and management of hereditary hemorrhagic telangiectasia were identified.[14] The methodological quality of the guidelines was independently assessed by three evaluators using the AGREE II tool. The overall AGREE II Score was 83% (Dimension 3: 85%; Dimension 6: 100%), therefore the guidelines were accepted, having exceeded the minimum acceptance threshold of 60% (Dimensions 3 and 6: threshold 50%) required by the CNEC Operating Manual, version 3.02 - February 2020.

The panel of authors decided to adopt without any modification the original recommendations of the international guidelines relating to the 5 clinical questions identified, having verified that these recommendations are up-to-date, reliable, acceptable by patients/family members and patient associations, applicable and implementable. in the Italian context.

Question 1
How should the diagnosis of HHT be made?

To confirm the diagnosis of hereditary hemorrhagic telangiectasia, Curaçao criteria are used which include: recurrent spontaneous epistaxis, presence of mucocutaneous telangiectasia, presence of visceral arteriovenous malformations, positive family history for the disease.

The diagnosis is confirmed with the presence of at least three of the criteria. With the presence of two out of four criteria, the disease is suspected, while the presence of fewer than two criteria allow the diagnosis of HHT to be considered unlikely. The diagnosis can be confirmed even in the absence of the Curaçao criteria by making use of the positivity of the genetic investigation.

Following confirmation of the diagnosis, a genetic investigation is performed to identify the mutated gene. The research is also extended to the patient's family members as a screening aimed at identifying asymptomatic or poorly symptomatic cases. The genetic defect is identified in 80-85% of cases.

INTERPRETATION OF THE DATA

To answer question 1, reference was made to the second international guidelines for the diagnosis and management of hereditary hemorrhagic telangiectasia.[14]

Recommendations

1. Diagnosis of HHT must be made using the Curaçao criteria or by identifying a causal mutation.
Evidence quality: very low
Strength of recommendation: weak in favor

2. It is recommended that clinicians consider the diagnosis of HHT in patients with one or more Curaçao criteria.
Evidence quality: very low
Strength of recommendation: weak in favor

3. Asymptomatic children of a parent with HHT should be considered carriers of possible HHT, unless the diagnosis is ruled out by genetic testing.
Evidence quality: very low
Strength of recommendation: weak in favor

4. The Panel recommends that physicians refer patients to genetic research of the mutations responsible for HHT in order to:
a) identify the causal mutation in a family with a clinically confirmed diagnosis of HHT;

b) establish a diagnosis in the relatives of a patient with a known mutation, including asymptomatic or minimally symptomatic individuals and individuals who express a willingness to perform prenatal testing;
c) establish a diagnosis of HHT in subjects who do not meet the clinical diagnostic criteria.
Evidence quality: very low
Strength of recommendation: weak in favor

5. For patients who test negative for ENG and ACVRL1 mutations, testing for mutations in SMAD4 should be considered in order to identify the causative mutation.
Evidence quality: very low
Strength of recommendation: weak in favor

Question 2
How should epistaxis be managed in HHT patients?

Epistaxis is a consequence of the presence of mucous telangiectasias in the nasal mucosa whose typically fragile walls break easily in the face of minimal thermal or mechanical insults. Some patients have infrequent and minor nosebleeds, while others may manifest serious pictures that cause profound anemia, significantly affecting the patient's quality of life.[6] Spontaneous and recurrent epistaxis are of variable magnitude and frequency and occur on average around 12 years of age or in any case prior to 21 years of age in almost all cases. [7]

The management of nosebleeds starts with the patient's correct information on home management, recommending the use of nasal ointments and humidification of the home environment. Topical therapies are used to treat mild nosebleeds. The drug that can be used for this purpose IS tranexamic acid. Some authors have also proposed the local injection of sclerosing substances with encouraging results, albeit performed on small series.

Among the surgical options, as the first choice, endoscopic, minimally invasive treatments are preferable with the aid of delicate instruments (Argon-Plasma or laser) that allow the selective treatment of nasal telangiectasias, resulting well tolerated and repeatable.[16] The intervention of septodermoplasty, one of the first proposed interventions, today finds limited indications, acting only on lesions localized at the level of the nasal septum.

In refractory cases, with important impairment of the quality of life, surgical closure of the nasal cavities may be proposed. This irreversible method must be taken into consideration in case of failure to respond to all other less invasive treatments.[17, 18]

Systemic therapies involve the use of drugs which, due to their formulation, can cause a series of side effects. On the medical side, new and recent lines of research have developed therapies directed against factors involved in the pathogenetic mechanisms of HHT using molecules such as Bevacizumab and Thalidomide.

Bleeding oral telangiectasias can be treated with the aid of laser photocoagulation in multiple sessions.[17]

INTERPRETATION OF THE DATA

To answer question 2, reference was made to the second international guidelines for the diagnosis and management of hereditary hemorrhagic telangiectasia. [14]

Recommendations
1. Patients with HHT-related epistaxis are advised to use topical moisturizing therapies that moisten the nasal mucosa to reduce epistaxis.
Quality of evidence: moderate
Strength of recommendation: strong in favor

2. Consider using oral tranexamic acid for the management of epistaxis unresponsive to topical moisturizing therapies.
Quality of evidence: moderate
Strength of recommendation: strong in favor

3. In patients who have failed to respond to topical moisturizing therapies, consider ablative therapies for nasal telangiectasias, including laser treatment, radiofrequency ablation, electrosurgery, and sclerotherapy.
Quality of evidence: moderate
Strength of recommendation: weak in favor

4. The use of systemic antiangiogenic agents should be reserved for the management of epistaxis that do not respond to topical moisturizing therapies, ablative therapies and / or tranexamic acid.
Quality of evidence: moderate
Strength of recommendation: strong in favor

5. Septodermoplasty may be indicated for patients whose epistaxis has not responded sufficiently to topical moisturizing therapies, ablative therapies and / or tranexamic acid.
Evidence quality: low
Strength of recommendation: weak in favor

6. The closure of the nasal cavities is an intervention to be reserved for patients whose epistaxis has not responded sufficiently to topical moisturizing therapies, ablative therapies and / or tranexamic acid.
Quality of evidence: moderate
Strength of recommendation: strong in favor

7. It is necessary that HHT patients with epistaxis who want specific treatment are referred to specialized cen-

ters with experience in the management of HHT-related epistaxis for a specific assessment and personalized treatment.
Evidence quality: very low
Strength of recommendation: weak in favor

8. The management of acute epistaxis requires the use of haemostatic material that has a low probability of causing new bleeding with its removal.
Evidence quality: very low
Strength of recommendation: weak in favor

Question 3
What are the most appropriate diagnostic procedures and therapeutic approaches for hepatic AVMs in HHT patients?

Hepatic AVMs are nearly asymptomatic or show only a slight increase in GGT in 90% of cases. More rarely, an arterial-portal shunt can give complications such as portal hypertension, porto-pulmonary hypertension,[10] ascites, encephalopathy and hematemesis [10] or complications such as heart failure and necrotizing cholangitis due to theft of the arterial supply.[11] Instrumental diagnostics of hepatic vascular malformative lesions is recommended in patients with a confirmed diagnosis of HHT, while in patients with suspected HHT it can be of assistance in diagnostic confirmation.

Screening techniques can be Doppler ultrasound, multiphase CT with contrast medium and MRI.

Liver ultrasound is a non-invasive and free of complications procedure and it is the examination of choice for the identification of hepatic AVMs, for diagnostic, therapeutic and prognostic purposes. MRI and CT are of second choice and reserved for selected cases. MRI of the abdomen, in particular with contrast medium, has a lower applicability due to the high costs and the need for patient collaboration, as well as for the possible need for sedation in pediatric age. CT with contrast medium is certainly a shorter examination but exposes to ionizing radiation. Angiography, performed by catheterization, has traditionally been considered the diagnostic "gold standard," but it is an invasive test, and therefore more rarely used.

Gastroscopy/colonoscopy are indicated in cases of chronic anemia not related to epistaxis or in the presence of melaena or hematemesis.

INTERPRETATION OF THE DATA

To answer question 3, reference was made to the second international guidelines for the diagnosis and management of hereditary hemorrhagic telangiectasia.[14]

Recommendations
1. Screening for liver AVMs should be offered to adults with certain or suspected HHT.
Evidence quality: low
Strength of recommendation: weak in favor

2. Diagnostic tests for hepatic AVMs should be performed in patients with HHT with symptoms and / or signs indicative of complicated hepatic AVMs (including heart failure, pulmonary hypertension, abnormal cardiac markers, liver function test abnormalities, abdominal pain, portal hypertension or encephalopathy), using Doppler ultrasound, multiphase CT with contrast, or abdominal magnetic resonance with contrast media for diagnostic evaluation of hepatic AVMs.
Quality of evidence: high
Strength of recommendation: strong in favor

3. Intensive first-line management should be reserved only for patients with complicated and / or symptomatic hepatic AVMs, adapted to the type of AVM incurring complications. HHT patients with high-output heart failure and pulmonary hypertension should be cared for by a HHT Center of Excellence and an HHT-trained cardiologist or pulmonary hypertension clinic.
Quality of evidence: moderate
Strength of recommendation: strong in favor

4. The prognosis of hepatic AVMs should be estimated using available predictors to identify patients who need closer monitoring.
Quality of evidence: moderate
Strength of recommendation: strong in favor

5. Consider infusion of bevacizumab intravenously in patients with symptomatic high-output heart failure due to hepatic AVMs who have not responded sufficiently to first-line management.
Quality of evidence: moderate
Strength of recommendation: strong in favor

6. Liver transplantation may be considered for patients with symptomatic complications of hepatic AVMs, particularly high-output refractory heart failure, biliary ischaemia, or complicated portal hypertension.
Quality of evidence: moderate
Strength of Recommendation: Strong in favor

7. It is recommended that liver biopsy be avoided in any patient with known or suspected HHT.
Evidence quality: very low
Strength of recommendation: strong in favor

8. Avoid hepatic artery embolization in patients with he-

patic AVMs as it is characterized by temporary efficacy and significant risk of morbidity and mortality.
Evidence quality: very low
Strength of recommendation: strong in favor

Question 4
What are the most appropriate diagnostic procedures and therapeutic approaches for pulmonary AVMs in HHT patients?

Pulmonary AVMs are asymptomatic in most cases, but can complicate dyspnoic and hypoxemic pictures caused by arteriovenous shunts (complications that can occur especially after the fourth decade). The presence of shunts allows the occurrence of paradoxical embolisms of various kinds (bacterial, gaseous, from a deep vein thrombosis, etc.) which can determine pictures of ischemia or brain abscesses.[8] Following the diagnostic confirmation and / or identification of the mutation, it is appropriate to perform some clinical and instrumental investigations aimed at searching for any arteriovenous malformations. Bubble echocardium and chest CT are tests aimed at looking for any pulmonary shunts and AVMs or to detect early pulmonary hypertension. If the tests are negative, they will be repeated after 5 years. In the presence of a positive response, each case is entrusted to multidisciplinary evaluation to establish a therapeutic indication or initiate the patient to follow-up with the aim of monitoring lesions that over time can reach such dimensions as to deserve treatment. Embolization is the treatment of choice for pulmonary AVMs in adults and children and allows long-term benefits to be obtained, if performed in referral centers for the disease.[1, 2] There is no data to support one endovascular technique better than another; the use of plugs or spirals or other embolizing agents is mainly dependent on the characteristics of the lesion and the experience of the center. The selection of cases to be treated by embolization is based on the diameter of the afferent arteriole, generally equal to or greater than 3 mm. For patients with untreated small pulmonary AVMs or dubious or microscopic lesions, the follow-up period should be determined on a case-by-case basis (between one and five years).

INTERPRETATION OF THE DATA

To answer question 4, reference was made to the second international guidelines for the diagnosis and management of hereditary hemorrhagic telangiectasia.[14]

Recommendations
1. All patients with certain or possible HHT for pulmonary AVM should be screened.
Evidence quality: very low
Strength of recommendation: strong in favor

2. Transthoracic echocardiography with contrast medium should be used as an initial screening test for pulmonary AVMs.
Evidence quality: low
Strength of recommendation: weak in favor

3. The treatment of choice for pulmonary AVMs is catheter embolization.
Evidence quality: low
Strength of recommendation: strong in favor

4. Patients with documented pulmonary AVMs (treated and untreated) should be adequately informed about the following long-term advice:
a. Antibiotic prophylaxis for procedures with risk of bacteremia
b. When placing a venous access, pay particular attention to the air inlet
c. Avoid scuba diving
Evidence quality: very low
Strength of recommendation: weak in favor

5. Long-term follow-up should be planned for patients with pulmonary AVMs to monitor the growth of untreated pulmonary AVMs as well as reperfusion of previously treated AVMs.
Evidence quality: low
Strength of recommendation: strong in favor

Question 5
What are the most appropriate diagnostic procedures and therapeutic approaches for brain MV in HHT patients?

Cerebral vascular malformations (10-20%, most common in HHT1) can be asymptomatic or cause cerebral hemorrhages, headache, transient or progressive clinical deficiency disorders and epileptic-type irritations.

Cerebrovascular malformations (CVM) differ according to the HHT genotype and there are several subtypes: arteriovenous malformations (AVM), arteriovenous fistulas (AVF), capillary telangiectasias and cavernous malformations. Patients may also have venous development abnormalities (DVA) and/or intracranial aneurysms.

Currently available therapies for cerebrovascular malformations include endovascular embolization, surgical resection, radiosurgery, or a combination of these. These are invasive procedures that involve a non-negligible risk of complications and clinical sequelae, the indication of

which must be based on the clinical picture and the analysis of risk factors and natural history. The cerebral vascular anomalies characterized by a particular higher risk of hemorrhage in patients with HHT are "large" (>2 cm) and "giant" (>2.5 cm) aneurysms and high-flow arteriovenous fistulas. Both of these injuries occur much more frequently (almost exclusively, possibly due to the low survival rate) in the neonatal population. Most of these lesions, due to their large size, can be seen with a simple ultrasound of the head in the newborn in its first days of life or before birth with fetal ultrasound and MRI studies.

Brain VMs are a frequent finding in adults with HHT, but the risk of bleeding is lower than in the newborn.[23]

Spinal AVMs are significantly less frequent (<1% of cases) than brain AVMs and may become clinically evident with hemorrhages, compression disturbances or as nonspecific pain in the spine or radicular irradiation.[6]

INTERPRETATION OF THE DATA

To answer question 5, reference was made to the second international guidelines for the diagnosis and management of hereditary hemorrhagic telangiectasia.[14]

Recommendations

1. MRI with and without contrast medium, using sequences that detect blood degradation products, is the examination of choice for screening of brain VM in adults with certain or suspected HHT.

Evidence quality: very low

Strength of recommendation: weak in favor

2. Adults with acute hemorrhage secondary to rupture of cerebral VM should be treated at a center with neurovascular expertise for definitive treatment.

Evidence quality: very low

Strength of recommendation: strong in favor

3. All patients with cerebral VM should be referred to a center with neurovascular skills for the performance of further investigations and any indication for personalized treatment.

Evidence quality: very low

Strength of recommendation: strong in favor

4. Pregnant women with certain or suspected HHT diagnosis who have asymptomatic brain VM should undergo definitive treatment of brain VM after delivery. The expert group recommends that childbirth follows obstetric principles.

Evidence quality: very low

Strength of recommendation: weak in favor

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Cobb syndrome

Definition

Cobb syndrome is characterized by the association of venous/arteriovenous vascular anomalies with metameric distribution with involvement of the spinal cord, vertebrae, soft tissues and skin; sometimes there can be visceral involvement. The segments most frequently involved are between T3 and T9.

Epidemiology

It is extremely rare with less than 100 cases reported in the literature.

Etiopathogenesis

The etiopathogenesis is unknown. No chromosomal abnormalities have been reported. It is not familiar and it is not hereditary. The pathogenesis is linked to alterations of vascular precursors present in the early stages of embryogenesis before their metameric migration, from the spinal cord to the skin. Metamers involved can be one (metameric) or some (multi-metameric) for which the term "Metameric spinal arteriovenous syndrome 1-31 (SAMA 1-31)" has also been introduced.

Clinical aspects

It usually begins in childhood and adolescence, regardless of gender and race, with neurological symptoms, especially asymmetric, sensory or motor deficits, related to bleeding episodes or chronic blood congestion in the spinal cord. Muscle and bone injuries can be asymptomatic or cause pain.

The course of the disease is unpredictable and lesions can remain asymptomatic for long periods of time.

Cobb syndrome is diagnosed when patients have three or more of the following changes:

- intramedullary arteriovenous vascular malformations;
- intra-spinal epidural vascular anomalies;
- vertebral vascular anomalies;
- paravertebral vascular anomalies.

Vascular cutaneous/subcutaneous anomalies ("port wine" stains, more rarely angiokeratomas, lymphatic).

Diagnosis

MRI and CT angiography of the whole spine are recommended for diagnostic purposes.

Treatment

The therapeutical strategies may be: medical therapy, with corticosteroids, laser treatment for skin vascular abnormalities, embolization and surgical resection of the AVM in selected cases.[1-3]

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Blue rubber bleb noevus (BRBN) or Bean syndrome

Definition

Blue Rubber Bleb Nevus syndrome (BRBN) is typically associated with a venous malformation characterized by skin lesions normally present at birth, varying in size and bluish in color, compressible and rubbery. The lesions are generally multiple and disseminated, with possible visceral involvement (mainly at the gastrointestinal level, especially in the small bowel).[1] It is associated with anemia, iron deficiency, reduction of blood fibrinogen values and elevation of serum D-dimer. The involvement of the central nervous system is rare. The lesions are usually asymptomatic, however in some cases they have been described as painful.[2]

Etiopathogenesis

It is an extremely rare syndrome with about 200 documented cases reported in the literature. It is included in the Rare Diseases list. It is a sporadic syndrome although families have been described in which an autosomal dominant hereditary transmission has been highlighted.[2] The mutated gene encodes for a tyrosine kinase receptor called *TEK* (TIE2 gene)[3] and it has been identified on the short arm of chromosome 9. The alteration in this gene is related to an increase in the mTOR pathway, leading to an increase in cell growth and angiogenesis.

Clinical aspects

Possible multiple disease locations determine an imaging diagnostic approach in addition to clinical monitoring. For gastrointestinal localization (frequent in addition to skin involvement) abdominal angio-resonance, gastro-colonoscopy, video magnetic capsule,[4] blood crase monitoring (lesions are typically associated with micro-bleeding) are used;[5] neuro-CT/MRI are helpful to find possible suspicious localizations in the CNS.

Question 1
Is it appropriate to perform imaging and blood chemistry investigations in patients suspected of BRBN syndrome compared to clinical evaluation alone for the diagnosis and certification of BRBN disease?

INTERPRETATION OF THE TESTS

To answer question one, two case reports and two case series have been identified in the literature which considered patients with BRBN and which report the importance of an in-depth imaging and blood chemistry for the diagnosis and certification of the disease, in addition to the evaluation of a potential extra cutaneous or gastrointestinal involvement.[1, 2, 5, 6]

The conclusions of the analyzed studies are consistent with each other to a high degree. There is agreement of outcome and evaluation method with integration of the imaging study and blood chemistry investigation within the screening and follow-up process. Diagnostic interventions make possible to identify visceral localizations. The scarce invasiveness of the imaging and blood chemistry methods associated with the possibility of an in-depth diagnostic analysis of fundamental importance in the management of BRBN places the cost/benefit ratio in favor of the patient, guaranteeing an awareness of possible complications.

Recommendations
For the purposes of diagnosis and certification of BRBN, it is indicated that the clinical-anamnestic examination is completed by an in-depth examination via imaging and blood chemistry (blood crasis).
Strong recommendation in favor, level of evidence 3

Treatment

Treatment options include surgery (particularly in intestinal occlusive complications), endoscopic laser photothermocoagulation or argon plasma, medical therapy (that includes Sirolimus/Rapamycin).[7]

Sirolimus, a specific mTOR inhibitor, has shown excellent therapeutic efficacy, defining itself as the drug of choice in the treatment of disseminated and complex forms.[8] The drug, despite being characterized by a good efficacy and safety profile, even in the pediatric population, requires careful monitoring conducted in a specialist center.

Question 2
In patients with BRBN is it indicated to evaluate the treatment with Sirolimus (Rapamycin) compared to the use of other medical-surgical methods in order to obtain an improvement in the skin and visceral clinical condition while maintaining a good safety profile?

INTERPRETATION OF THE DATA

To answer question two, a systematic review, two cohort studies, two case reports and four case series were identified in the literature describing the efficacy and tolerability of treatment with Sirolimus (Rapamycin) in patients with BRBN.[1, 2-9]

The conclusions of the analyzed studies are consistent with each other to a high degree and with confirmation of the therapeutic role of Sirolimus. The latter argue on therapeutic efficacy and safety for the population under consideration and use a direct comparison of the results.

Immunosuppressive therapy, even if not resolving and while increasing the infectious risk, is the only one capable of obtaining good results and able to counteract the evolution of the disease. It should be reserved for those patients in whom it is not possible to practice surgical therapy or where therapeutic abstention is not practicable.

All the studies analyzed, including a systematic review, agree in formulating the recommendation. The beneficial effects outweigh the undesirable effects achieving better results than other medical-surgical methods.

Recommendations
In patients with BRBN, treatment with Sirolimus (Rapamycin) could be indicated to obtain an improvement of the skin condition and a control of intestinal bleeding while maintaining a good safety profile.
Weak recommendation in favor, level of evidence 1 ++

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Maffucci Syndrome

Definition

Maffucci Syndrome is characterized by the association of multiple enchondromas and vascular anomalies.

Epidemiology

It belongs to the group of rare diseases and MS OMIM% 614569.

Etiopathogenesis

Maffucci Syndrome is sporadic, not hereditary, and correlated to the presence of somatic mosaic mutations of *PTHR1*, *IDH1* and *IDH2* genes.[1-3] Mutations of the *IDH* genes are also involved in the onset of various neoplasms: "spindle cell hemangiomas;" [4] juvenile granule cell tumor of the ovaries;[5, 6] gliomas, glioblastomas,[7] acute myeloid leukemia, T-cell lymphoma, intrahepatic cholangiocarcinoma,[1] angiosarcoma and pancreatic adenocarcinoma.[8]

Clinical aspects

Maffucci Syndrome is characterized by the presence of enchondromas localized in particular in the bones of the hands, more rarely at the skull base (13%) [9] with possible malignant evolution (chondrosarcomas), associated with vascular anomalies, in particular venous and, more rarely, "spindle cell hemangiomas." Vascular anomalies can occur before or after the onset of enchondromas. When the enchondromas are firstly observed, the Maffucci Syndrome can be erroneously classified as Ollier Syndrome, a syndrome which, unlike the Maffucci Syndrome, does not present vascular anomalies, but only multiple enchondromas. Finally, it should be remembered that the vascular anomalies of Maffucci Syndrome can also be localized in the visceral area.

Diagnosis

Diagnosis is based on clinical picture, conventional radiology and nuclear magnetic resonance.
For the purposes of diagnosis and certification of Maffucci Syndrome, in addition to the clinical-anamnestic examination and non-invasive radiological diagnostics, a histopathological and genetic-molecular framework may be indicated.

Treatment

It includes surgical excision of vascular malformations and enchondromas and reduction of secondary fractures in the presence of enchondromas.[10]

Question 1
In patients with suspected Maffucci Syndrome, which instrumental investigation is indicated for the identification of chondromas/chondrosarcomas and vascular anomalies?

Total body MRI is recommended at the time of diagnosis for a complete evaluation of both bone and/or cartilage lesions and vascular anomalies.

INTERPRETATION OF THE DATA

To answer QUESTION 1,[11] the only work available in the literature was analyzed. This work is a review of previously described clinical cases associated with data from the authors.

It indicates MRI as an instrumental examination relevant to differentiate MS from Ollier's disease. In fact, although they are very similar diseases, they have differences with regard to the onset of malignancy. The work has limitations related to the lack of a review of radiographic and histological data with regard to the reviewed cases.

Recommendations
In patients suspected of having Maffucci Syndrome, a total body MRI may be indicated.
Weak recommendation in favor, level of evidence 4

Question 2
In patients with Maffucci Syndrome, which follow-up is indicated for the early identification of any complications?

In pediatric age, clinical examination is recommended every 6-12 months and radiography of bone lesions every

2-3 years for early diagnosis of growth anomalies to be subjected to surgery.

In adults, periodic clinical (12-24 months) and radiographic examinations of bone lesions (2-3 years) are recommended for the early diagnosis of malignant transformation of bone lesions.

From the age of 30 and in the case of enchondromas with a diameter> 5-6 cm, periodic (annual) total body MRI is recommended for the early diagnosis of malignant neoplasms in the extraskeletal area.

Bone scan and CT scan can be alternatives to MRI in particular cases.

INTERPRETATION OF THE DATA

To answer question 2, the same work [10] used to answer question 1 was used which, therefore, has the limitations already mentioned.

Recommendations

In Maffucci Syndrome, careful follow-up may be indicated, including periodic clinical and radiological examinations for the early diagnosis of malignancy.

Weak recommendation in favor, level of evidence 4

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Capillary malformation syndrome with artero-venous malformations (CM-AVM)

Definition

Capillary-arteriovenous malformation syndrome (CM-AVM) is clinically characterized by multiple round brownish-red skin macules of 1-3 cm in diameter, rarely exceeding 15 units. The lesions may already be present at birth and progressively increase in number over the course of life. They typically begin with a white vasoconstriction halo.[1] In about 30% of patients, AVM and arteriovenous fistulas, high flow, localized at the level of the central nervous system, skin and subcutis, at the level of muscles and/or bones, of the face, neck, end. Their finding is associated with an increase in mortality and morbidity.[2]

Etiopathogenesis

The syndrome is autosomal dominant, with high penetrance and a wide phenotypic variability, even within the same family nucleus. This is an extremely rare entity with a prevalence of 1/10,000 patients.[3] CM-AVM syndrome can be caused by mutations in *RASA1* gene, implicated in type 1 CM-AVM, or in *EPHB4* gene, implicated in type 2 CM-AVM.[4] This latest variant of CM-AVM has recently been defined and has a similar appearance to CM-AVM 1 and can present an overlapping with HHT (hereditary hemorrhagic telangiectasia). CM-AVM 2 shows a lower risk of high flow vascular anomalies in the central nervous system, and in any case deserving of follow-up over time.[5-7]

Clinical aspects

The histological features of associated skin lesions have been described in the literature as characterized by minimally dilated cutaneous vessels in the mid-upper dermis, with or without endoluminal erythrocytes.[8, 9]

Recent histological analyzes [3] suggest that the skin component typical of CM-AVMs differ from malformations of capillary nature both for histological and immunohistochemical characteristics. On the other hand, more similarities can be seen with respect to arteriovenous malformations of which the CM-AVM could represent an incipient phase. However, further studies are needed to confirm this first hypothesis.

For a correct diagnosis, a multidisciplinary approach is required that investigates the vascular component (using appropriate imaging methods, echo-Doppler, MRI), the skin component (epiluminescence), the genetic-histological characteristics (RASA1/EPHB4).[10-12]

Le caratteristiche istologiche delle lesioni cutanee associate sono state descritte in letteratura come caratterizzate da vasi cutanei minimamente dilatati nel derma medio-superiore, con o senza riscontro di eritrociti endoluminali.[8, 9]

Question 1
In CM-AVM patients, is an evaluation with dermatoscopy/epiluminescence indicated in a reference center for a correct differential diagnosis from other simple and complex vascular malformations?

INTERPRETATION OF THE DATA

To answer question 1, a case series was identified in the literature that considered patients with CM-AVM and which reported the importance of the epiluminescence method for a correct differential diagnosis and for subsequent disease certification.[13]

The study under consideration is relevant for the target population, the evaluation with epiluminescence plays a relevant role in the differential diagnosis. The benefit of the recommendation is to favor a correct differential diagnosis of CM-AVM through a non-invasive and easy-to-use method, which is also part of a routinal dermatological evaluation. The intervention is acceptable compared to the control, considering the non-invasiveness and speed of the method.

Recommendations
For a correct differential diagnosis of CM-AVM compared to other vascular malformations, a specialist evaluation is indicated that includes dermatoscopy/epiluminescence at a Reference Center.
Strong recommendation in favor, level of evidence 3

Question 2
In patients with CM-AVM, are genetic counseling, histopathological examination and genetic-molecular tests on biopsy sampling of the pathological tissue necessary for the purpose of certifying a rare disease?

INTERPRETATION OF THE DATA

To answer question 2, 8 case series were identified in the literature describing patients with CM-AVM and which reported the importance of a genetic or histopathological study for the diagnosis and certification of the disease. All the studies analyzed agree in formulating the recommendation.

The benefit of the recommendation is to ensure a disease diagnosis of patients with suspected CM-AVM by identifying possible vascular malformations associated with the genetically related malformation subtype. The scarce invasiveness of the methods (biopsy of superficial skin lesion) associated with the possibility of an in-depth diagnostic analysis of fundamental importance in the correct diagnosis of the CM-AVM type places the cost/benefit ratio at a very low level. The specialized centers already present and operating on the national territory guarantee a short-term applicability of the recommendation with specialized geneticist and pathological anatomy personnel.

Recommendations
For the purposes of diagnosis and certification of CM-AVM, in addition to the clinical-anamnestic examination and non-invasive radiological diagnostics, a histopathological and genetic-molecular framework may be indicated.
Weak recommendation in favor, level of evidence 3

Treatment

We opt for endovascular surgery for the treatment of AVM, while for the treatment of the superficial component of the lesions recently some studies have shown a good response of the same to laser therapy with Pulsed Dye Laser.[14]

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Microcephalia-capillary malformation (MIC-CAP)

Definition

MICrocephaly CAPillary Malformation Syndrome.[1]

Epidemiology

Unknown. To date, 12 cases with molecular confirmation have been described.[1]

Etiology

Genetic condition caused by biallelic pathogenetic variants (mutations) in *STAMBP* gene (in each cell both copies of *STAMBP* gene have the mutation).

Transmission is autosomal recessive.[1]

Clinical aspects

Congenital onset of microcephaly, skin capillary malformations, intractable epilepsy and psychomotor retardation.

Microcephaly is present from birth. Neuroradiological images show an increase in periencephalic spaces, simplified gyration and progressive cerebral atrophy. Hyppocampal hypoplasia, corpus callosum hypoplasia, hypoplasia of the optic nerves and optic chiasm may also be present. Cutaneous capillary malformations are usually distributed to the scalp, trunk, limbs and genitals.[2]

Early-onset epilepsy, generally in the first day of life, is pharmacologically intractable in many of the patients. It tends to become less severe and therefore also more treatable after two years of life.

Psychomotor retardation and consequent intellectual disability is severe in most patients. Severe central hypotonia is present.

Anomalies of the fingers and toes (hypoplastic or absent phalanges and nails) and of the face (receding forehead, hypertelorism, epicanthus, elongated eyelids, ptosis, low-implant auricles, micrognathia) may be associated.

Movement disorders (myoclonus of the limbs and eyelids), feeding difficulties, pre- and postnatal growth retardation, short stature, deafness, renal and cardiac malformations are described.[1, 3, 4, 5]

Diagnosis

Diagnosis is based on clinical and neuroradiological features. The clinical diagnosis is confirmed by the identification of mutations in *STAMBP* gene.

Magnetic resonance imaging of the brain, evaluation by the child neuropsychiatrist, ophthalmological evaluation, ENT evaluation, cardiological evaluation with echocardiography and abdomen ultrasound are indicated.[1]

Evaluation of clinical genetics for the genetic-molecular framework.

Treatment

The treatment is mainly rehabilitative. Pharmacological treatment of epilepsy associated with neurological follow-up.[1]

Follow-up is multidisciplinary with the involvement of different specialists according to clinical needs.

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Cutis marmorata teleangiectasica congenita (CMTC)

Definition

Congenital Telangiectatic Cutis Marmorata (CMTC) is described as a persistent diffuse reticular capillary malformation on atrophic (sometimes ulcerated) skin with demarcation to a hemisome associated with hypotrophy of a limb or the entire hemisome.[1]

It is included in the Rare Diseases list.

Etiopathogenesis

For the first time described by the Dutch pediatrician Cato van Lohuizen in the early 1900s, it has been reported in the literature under different names: hereditary congenital phlebectasia, reticular vascular nevus, congenital phlebectasia, congenital reticular livedo, and van Lohuizen syndrome. Etiology of disease remains unknown to date, recent studies have identified mutations in GNA11 gene from biopsies performed on skin tissues affected by CMTC. The same mutation to date is difficult to identify, if not in extremely low percentages, even in the blood.[2]

Clinical aspects

Capillary and venular nature of disease characterize a low vascular flow. Although it usually has a benign evolution, it can be associated with ocular abnormalities (from glaucoma to decreased vision with potential vision loss), limb asymmetry and central nervous system involvement that require medical attention.[1] Histopathologic examination currently plays a minor role, making the diagnosis of CMTC of a clinical nature.[3]

Diagnosis

In addition to the direct evaluation of vascular anomalies by Doppler ultrasound, it is fundamental to monitor possible comorbidities by multidisciplinar approach.

In particular, it is important to monitor the ocular picture over time with ophthalmological follow-up[4] (including the shapes not necessarily distributed to the face) in addition to the constant evaluation of the vascular-cutaneous component of the affected area.

Treatment

The therapeutic approach is conservative nature.

Question 1
In CMTC patients, is a multidisciplinary follow-up that includes an ophthalmological evaluation indicated, as opposed to a mono-specialist evaluation, in order to exclude a visceral involvement?

INTERPRETATION OF THE DATA

To answer Question one, a systematic review, two case reports and a case series were identified in the literature which considered patients with CM-AVM and which reported the importance of a multi-specialist evaluation, and in particular an ophthalmologic one, to exclude visceral vascular involvement.[1-4]

The studies under consideration are relevant to the target population with outcome agreement and assessment methodology with integration of the ophthalmological assessment within the screening and diagnostic follow-up process. High degree of coherence between studies.

The studies are relevant to the target population, argue about comorbidities relevant to the target population and use a direct comparison of the results. The benefit of the recommendation is to ensure a better overall assessment of patients with suspected CMTM in order to prevent potential harm associated with the presence of unrecognized visceral abnormalities. Integrated multi-specialist assessment, and in particular ophthalmologic, would guarantee a multidisciplinary assessment without resorting to methods judged to be invasive. All the studies analyzed, including a systematic review, agree in formulating the recommendation. The desired effects clearly outweigh the undesirable effects in relation to the low invasiveness of the method and the important benefits associated with early ophthalmological evaluation.

Recommendations
To rule out visceral involvement in patients with CMTC, a multidisciplinary evaluation including an eye examination with evaluation of ocular tonometry and fundus oculi is indicated.
Strong recommendation in favor, level of evidence 1 ++

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Guidelines for lymphatic malformations

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Definition and classification

Lymphatic malformations (LM) are embryogenetic errors of lymphangiogenesis that are further subdivided into two subgroups (Hamburg Classification, 1988) on the basis of both anatomical and embryological criteria: Extratruncular and Truncular forms.

Extratruncular LM: these are embryonic residues due to arrested development in the early stages of embryogenesis. They are composed of "immature" vascular tissue of the mesenchymal type which retains the potential for growth if stimulated (menarche, pregnancy, hormonal therapies, trauma, infections, surgery).

Truncular LM: they are errors of later stages of angiogenesis. This is "mature" vascular tissue that has lost its growth potential when stimulated.

The Classification of the "International Society for the Study of Vascular Anomalies - ISSVA" (Rome, 1996) has divided the MLs as follows:

- Extratruncular LM:
  - a) macrocystic (synonym old classification: cystic hygroma)
  - b) microcystic (synonym old classification: lymphangioma)
  - c) combined (micro- and macro-cystic)
- Truncular LM:
  - primary lymphedema
- Syndromic LMs:
  - a) Hennekam;
  - b) Gorham Stout;
  - c) Lymphedema-cholestasis;
  - d) GLA (generalized lymphatic anomaly).

There have been two subsequent revisions, respectively in 2014 and 2018, so the ISSVA classification, which currently has international consensus, is the following:

- a) Common (cystic) lymphatic malformations
  - macrocystic;
  - microcysts;
  - mixed.
- b) Lymphangiomatosis or Generalized Lymphatic Anomaly (GLA)
- c) Lymphatic malformations of Gorham-Stout Syndrome (GSD, Gorham Stout Disease)
- d) Kaposiform Lymphangiomatosis (KLA, Kaposiform Lymphangiomatosis)
- e) Truncular lymphatic malformations: primary lymphedema, of which the following forms are known:
  - Nonne-Milroy's disease;
  - hereditary primary lymphedema;
  - lymphedema -dystichiasis;
  - hypotrichosis-lymphedema-telangiectasia;
  - primary lymphedema with myelodysplasia;
  - primary generalized lymphatic anomaly (Hennekam syndrome);
  - microcephaly with or without chorioretinopathy and lymphedema;
  - lymphedema and choanal atresia.
- f) Other rare forms: Central Conducting Lymphatic Anomaly (CCLA).

Recommendations

The identification of the embryological subtype (truncular or extratruncular) of a lymphatic malformation allows the initial orientation towards the correct clinical-instrumental and therapeutic path.

Recommendation of good clinical practice

Extratruncular (or common) lymphatic malformations of the macrocystic type

Definition

In literature, macrocystic ones are defined as those LMs consisting completely or predominantly of cysts with a diameter greater than 1-2 cm, and microcystic those LM consisting completely or mainly of cysts that have a diameter of less than 1 or 2 cm or, in any case of such dimensions, that they cannot be aspirated or treated with sclerotherapy.[1-3]

Other authors define as macrocystic those LM presenting a prevalence (>50%) of cysts with a diameter greater than 2 cm; microcysts those LM that do not have cysts greater than 2 cm in diameter; mixed those LM that have a prevalence (>50%) of cysts less than 2 cm.[4]

Etiology

The etiology of extratruncular LM is still unknown. At the moment, a genetic approach is not yet possible as they occur sporadically without hereditary transmission. The same goes for the rare forms such as GLA and GSD. Instead, in primary lymphedema, a paradigmatic expression of truncular ML, at least one aberrant gene has been identified for all known forms (see related chapter).

Epidemiology

The global incidence of vascular anomalies in the general population is not exactly known.

The global incidence of vascular malformations as a whole is currently estimated at around 1.2%, while the incidence of lymphatic malformations fluctuates approximately between 1 and 5 cases per 10.000 inhabitants.[5, 6]

Histology

Extra-truncular LMs are histologically characterized by vascular spaces of variable diameter and, on the basis of this parameter, can be distinguished into microcystic, when the diameter of the dilated vessels is less than 5 mm, and macrocystic, when the diameter is greater than 5 mm. Microcystic LMs have thin wall, with flat or slightly raised endothelium, surrounded by rare pericytes, without smooth muscle lining, while macrocystic ones have more frequently thickened and fibrous wall, with smooth muscle cells. The lumens of the lymphatic vessels contain lymph, characterized by an amorphous and clear appearance, rare lymphocytes and macrophages; sometimes they can contain red blood cells, in particular when they suffer trauma or when they are in connection with venous vessels; occasionally intraluminal valves may be present. The tissues in which LMs develop can be diffusely dissected by the vascular proliferation itself or be accompanied by fibrosis, with or without perivascular lymphocyte infiltrate. The endothelium has modest mitotic activity, detectable with the immunocytochemical marker Ki67, and lymphatic differentiation can be demonstrated by positivity to specific markers such as podoplanin (D2-40) and PROX-1.[7-10]

Natural history

In most cases, lymphatic malformations are evident from birth, although sometimes they manifest late (in 50% of cases they manifest clinically at birth and in 90% of cases in the first two years of life). The possibility of spontaneous regression is very rare, and must be considered as the result of inflammatory-infectious episodes that are responsible for obliteration of the cysts with secondary sclerosis and resorption.[11]

The size increase of the lesions is progressive and usually slow and proportional to somatic development, but episodes of acute volumetric increase secondary to intracystic hemorrhage are not rare 2 It is also possible to observe an exacerbation during puberty or pregnancy due to estrogen-dependent hormonal changes.[3, 12]

Clinical aspects

Question 1
What are the clinical manifestations that lead to the diagnosis of macrocystic lymphatic malformation?

The clinical picture is related to volume, site of the lesion and hemorrhagic/inflammatory and infectious complications. The most frequent sites are the cervico-facial region (in over 50% of cases), axillary region, face, chest wall and mediastinum. They have a tendency to gradually increase in volume over the years.

The diagnosis is usually suspected by the presence of a soft, compressible or tense-elastic swelling, not painful, with undamaged overlying skin.

If large, they can cause functional problems related to the site; the most severe problems are: respiratory distress and/or dysphagia in the cervical and mediastinal localizations; proptosis and visual disturbances in orbital localizations; abdominal pain for visceral ones.[1, 13]

The most frequent complication is endocystic hemorrhage, responsible for an acute volumetric increase of the malformation, with the onset of fever, local pain, an even conspicuous increase in the volume of the lesion and related symptoms of compression of the adjacent structures.[3]

LMs are already evident ultrasonographically in the prenatal period, and the clinical diagnosis (or suspicion) is easily reached in the neonatal period or in the first two years of life in 90% of cases, with the exclusion of rare visceral forms.[14-18] Sometimes the lesion may remain invisible and silent for years, and then manifest itself acutely, following a local inflammatory complication or endocystic hemorrhage, presenting itself as a tense-elastic, red and painful swelling.[2, 19, 20]

Even in the absence of complications, macrocystic LMs tend to progressively increase in volume. There are, however, sporadic reports in the literature of possible spontaneous regression, sometimes as a result of fibrosis secondary to inflammatory-infectious complications.[11]

The greatest risk of LM progression occurs during ad-

olescence, due to hormonal changes of puberty that can contribute to their expansion. And it is because of this risk of progression that some authors consider early therapy indicated, even in the presence of asymptomaticity.[12]

INTERPRETATION OF THE DATA

To answer Question 1, nine relevant articles have been analyzed, which together expose in a comprehensive and didactic way the salient clinical characteristics of macro-cystic lymphatic malformations: seven narrative reviews,[2, 3, 11, 12, 14, 16, 19] a retrospective cohort study[15] and a guideline.[1, 2, 3, 11, 12, 14-17, 19]

Recommendations

Careful history and complete physical examination allow the clinical diagnosis of macro-cystic lymphatic malformation in the majority of cases.

Recommendation of good clinical practice, based on the experience of the panel

Instrumental diagnostics

Question 2

In case of suspicion or clinical evidence of macro-cystic LM, which is the most suitable first-level instrumental investigation to confirm the diagnosis and to evaluate the anatomical characteristics of the malformation?

The first diagnosis (or diagnostic suspicion) is always clinical; it must be followed by an echo-color-Doppler evaluation to confirm the diagnosis and for an initial assessment of the extent of the lesion.

The echo-color-Doppler allows to document the presence of uni or multiloculated macrocysts, which appear iso- or hyperechoic, with possible liquid-liquid levels in case of intracystic hemorrhage, caused by the rupture of small septal vessels.

Vascularization is only present in the septa and absent within the cysts.[1, 11, 20]

INTERPRETATION OF THE DATA

To answer question 2, a guideline [1] and two narrative reviews of the literature [11, 20] were analyzed that consider ultrasonography as a reliable first level method in the diagnostic process.[1, 11, 20]

In the studies analyzed, the experts agree in defining the echo-color-Doppler as a first level instrumental examination for lymphatic malformations, as it allows an initial evaluation of the main morphological and extension characteristics of the malformation and its possible complications. The echo-color-Doppler is a non-invasive, low-cost, repeatable and non-traumatic investigation for the patient. It should preferably be performed by skilled personnel in the field. Studies are relevant to the target population.

Recommendations

For confirmation of the clinical diagnosis of macro-cystic lymphatic malformation and for an initial assessment of the extent of the lesion, it is recommended to perform echo-color-Doppler as a first-level non-invasive instrumental investigation.

Strong recommendation in favor, level of evidence 3-4

Question 3

In case of clinical and ultrasound diagnosis of macrocystic lymphatic malformation, what are the other instrumental investigations that allow us to better define the malformation in anticipation of therapeutic measures and/or monitoring over time?

Magnetic resonance

MRI allows to highlight the relationships of macrocysts with deep tissues and organs (mediastinum, pharynx, laryngotracheal axis, etc.), to visualize deep and visceral localizations and to allow the differential diagnosis with other pathologies with similar clinical presentation.[20]

The cysts present hypointense in the T1-weighted sequences and hyperintense in the fat-sat T2w sequences, with hypointense trabeculation corresponding to the septa. In case of hemorrhagic content, macrocysts may present hyperintense T1w signal with fluid levels.

After administration of contrast medium (gadolinium), only a septal impregnation is highlighted, allowing the differential diagnosis with respect to venous malformations which present the same signal in T1 and T2 fat-sat, in the absence of contrast medium.

Both T1-weighted and T2-weighted sequences also allow the differential diagnosis with respect to branchial cysts, lipomas, thyroglossal cysts, abscesses, thyroid masses.

In addition, MRI has the advantage of highlighting the margins and areas of infiltration, compared to ultrasound; this data is important as it allows to highlight the associated microcystic component, and therefore to diagnose mixed type LMs.[3, 9, 11, 20]

In case of peritoneal localizations, MRI allows the differential diagnosis with respect to cystic mesothelioma, neoplastic lesions with cystic components with mucinous or myxoid content, lymphocele, ascites, cysts with thickened walls or septa suggesting other pathologies.[1, 2, 13]

INTERPRETATION OF THE DATA

To answer question 3, six articles were identified: five narrative reviews [3, 11, 13, 20, 21] and an expert opinion.[3, 9, 11, 13, 20, 21]

The studies agree on the execution of an MRI as a second level instrumental examination after the echo-color Doppler. This investigation allows to complete the diagnostic evaluation of the macrocystic LM in terms of extension, involvement of the surrounding tissues and internal organs. The examination does not involve significant risks, but it requires anesthesia or sedation in children under 4-5 years of age. With the exclusion of the preschool child, MRI is easily feasible throughout the country, but the interpretation of the images should be performed by radiologists with expertise in the field.

Although the reference articles are few and the series of cases numerically limited, the relative studies are now consolidated over time, homogeneous, shared and reliable. They can therefore be considered relevant in defining MRI as a second-level investigation that is indispensable for therapeutic purposes for the target population. The conclusions are consistent and the benefits clearly outweigh the harms. Consequently, even in the presence of weak evidence, we can make a strong recommendation.

Recommendations
Magnetic Resonance is indicated for the diagnostic confirmation and for a precise balance of extension of the macrocystic LM in anticipation of therapeutic treatment.
Strong recommendation in favor, level of evidence 3-4

Computerized tomography (CT)

CT is indicated only in cases where MRI is contraindicated, and should be avoided especially in children, in order to minimize radiation exposure. While CT can help confirm the diagnosis, it does not provide all of the information on MRI.

INTERPRETATION OF THE DATA

There are not adequate studies to evaluate the scientific evidence of the role of CT in the diagnosis of macrocystic LMs.

Recommendations
Computed Tomography has few indications, and replaces MRI only in cases where MRI is contraindicated.
Recommendation of good clinical practice, based on the experience of the panel

Angiography

Angiography (phlebography, lymphography, lymphangiography) is an invasive investigation that does not provide any elements in favor of the diagnosis, has no indication and should be avoided.

INTERPRETATION OF THE DATA

There are no adequate studies to evaluate the scientific evidence of angiography in the diagnosis of macrocystic lymphatic malformations.

Recommendations
Angiography should not be performed.
Recommendation of good clinical practice, based on the experience of the panel

Biopsy

The biopsy is indicated in rare doubtful cases in which instrumental investigations do not allow the diagnosis of certainty for therapeutic purposes.

INTERPRETATION OF THE DATA

There are no adequate studies to evaluate the scientific evidence of the role of biopsy in the diagnosis of lymphatic malformations.

Recommendations
Biopsy is rarely indicated for diagnostic purposes, but must be performed whenever instrumental investigations do not allow the diagnosis of certainty.
Recommendation of good clinical practice, based on the experience of the panel

Prenatal diagnosis

Question 4
Is prenatal diagnosis of macrocystic lymphatic malformation possible?

Macro-cystic or mixed ML can be seen in the prenatal period after the first trimester of pregnancy. The operator, in the differential diagnosis, must always keep in mind the possibility, although rare, of a cystic lymphatic anomaly, which can manifest itself early and can evolve volumetrically quickly, in order to be able to recognize risk situations, especially in the case of cervical and / or thoracic malformative localizations.[15-17]

The limit of ultrasound is the difficulty of direct visualization of the laryngotracheal axis.

Instead, prenatal MRI allows, in addition to diagnosis, to

evaluate a precarious airway and therefore to define the need for therapeutic treatment at the time of delivery.[1, 14, 22-24]

Cystic LMs are caused by embryonic development errors that occur between the fourth and sixth week of gestation. They are often associated with aneuploidy, multiple congenital anomalies, polyhydramnios, fetal death in utero, syndromes such as Noonan, Turner and trisomies. When a cystic LM is early diagnosed in utero, it is frequently accompanied by other abnormalities and fetal loss. When a LM occurs late in pregnancy, aneuploidy and other structural abnormalities are way rarer.[25]

Early prenatal diagnosis of LM must be completed with the ascertainment of any chromosomal abnormalities.

In the presence of an abnormal karyotype (derived from amniotic fluid or chorionic tissue) and/or severe associated anomalies, it is important that the woman is taken care of by an obstetric and gynecological medical center (according to Italian law), to evaluate the possibility of voluntary termination of pregnancy after the first trimester.[22-24]

In conclusion, ultrasound monitoring of the lesion, fetal MRI in cervico-mediastinal localizations, karyotype and ultrasound search for other structural anomalies are indicated in the fetus with macrocystic (or mixed) LM.

INTERPRETATION OF THE DATA

To answer question 4, 7 studies concerning the possibility of fetal diagnosis of macrocystic lymphatic malformations were analyzed: five narrative reviews,[14, 16, 23-25] a retrospective cohort study [17] and a series of clinical cases.[15]

The conclusions of the analyzed studies are consistent with each other. Both echo-color Doppler and non-contrast MRI are non-invasive procedures, completely free from risks for the fetus and with no negative impact on pregnancy.

The feasibility of instrumental investigations is good on the entire national context. The studies are relevant to the target population and the benefits clearly outweigh the harms.

Recommendations

1. Macrocystic (or mixed) lymphatic malformations are susceptible to fetal ultrasound diagnosis after the first trimester of pregnancy; it is recommended to always keep in mind the possibility of cystic lymphatic malformation of the fetus in the differential diagnosis

Recommendation of good clinical practice, based on the experience of the panel

2. There is a risk of airway obstruction in macrocystic lymphatic malformations at cervical site; in this situation, fetal MRI without contrast is indicated, since ultrasound does not allow adequate visualization of the laryngotracheal axis of the fetus.

Strong recommendation in favor, level of evidence 3-4

3. In the case of early fetal diagnosis of macrocystic LM, the investigation of the karyotype of the fetus through amniotic fluid is indicated.

Recommendation of good clinical practice, based on the experience of the panel

Question 5

In case of prenatal diagnosis of macrocystic lymphatic malformation, which strategy should be adopted?

Whatever the location of the macrocystic (or mixed) LM diagnosed in the fetal period, the volumetric evolution of the malformation requires instrumental monitoring (ultrasound and MRI without contrast), being at risk of an unpredictable volumetric increase.[23, 24]

In the absence of deviation/compression of the airway, a cervical or cervico-mediastinal macrocystic LM with a diameter greater than 5 cm can be considered an indication for cesarean delivery.

In cases of macro-cystic LM in the cervical or cervico-mediastinal region, fetal MRI (without contrast) makes it possible to predict the need for therapeutic procedures at delivery in fetuses considered at risk of airway obstruction.

In particular, fetal MRI can predict the need for EXIT ("ex-utero intrapartum treatment"), evaluating the extent of contact between the malformation and the laryngotracheal axis, which should be precisely monitored. Tracheostomy should be considered when the LM is in contact with the airway and surrounds it for more than one hemicycle. Furthermore, the longer the contact extension, the more likely is the need for EXIT and tracheostomy.[26, 27]

The procedure defined EXIT involves general anesthesia of the mother, low transverse laparatomy and hysterectomy. The head, neck, upper thorax and one upper limb of the fetus are externalized, while the rest of the fetus body remains in the uterine cavity in order to maintain the uterine volume and the temperature of the fetus; in this way the fetus continues to receive placental support. The operative sequence includes: laryngoscopy with intubation; bronchoscopy with intubation; tracheostomy. Once the airway is secured, the umbilical cord is interrupted and the birth concluded. The newborn is then transferred to an intensive care unit for postnatal therapy of the malformation (surgery, sclerotherapy, drug therapy, or clinical surveillance only).[18]

According to some authors, the EXIT procedure should preferably be followed by sclerotherapy with bleomycin (at a dose of 0.5 mg/kg in aqueous solution) and not by

surgery, and they consider this procedure to be the first therapeutic option after EXIT, but in this regard there are not shared operating protocols available.[23, 24]

Chest wall LMs are much less frequent than cervical, mediastinal and axillary locations. For these sites there is no need to provide for EXIT-type procedures and natural childbirth can be allowed, compatibly with the volume of the malformation.[28]

Spontaneous involution of macrocystic LM is possible, both in utero and after birth, with a reported incidence of about 9%.[23, 24]

INTERPRETATION OF THE DATA

To answer Question 5, six articles were identified, of which five narrative reviews [18, 23, 24, 26, 27] and a series of cases.[28]

The studies analyzed agree on the need for instrumental monitoring of macrocystic (or mixed) lymphatic malformations diagnosed in utero, they agree on the delivery methods and the therapeutic measures to be undertaken and are reliable and consistent in the conclusions.

The quality of the evidence, assessed through the Checklists, was found to be good.

As for the feasibility of the procedures, the articles reported highlight how the treatment should be reserved for Centers with proven experience in childbirth assistance, equipped with neonatal intensive care units and with operators familiar with the treatment of vascular malformations in the neonatal period.

Recommendations

1. In case of prenatal diagnosis of cervico-mediastinal macro-cystic (or mixed) lymphatic malformation with obstruction of the airway, the EXIT ("ex utero intrapartum therapy") procedure with tracheotomy and subsequent intensive care treatment of the newbon are indicated.
Recommendation of good clinical practice, based on the experience of the panel

2. In case of fetal diagnosis of macrocystic (or mixed) lymphatic malformation associated with chromosomal abnormalities and other severe structural malformations, termination of pregnancy must be evaluated.
Recommendation of good clinical practice, based on the experience of the panel

Treatment

Question 6

What are the therapeutic procedures used for the treatment of macrocystic lymphatic malformation?

Macrocystic LMs tend to compress and displace the surrounding structures and has no infiltrating characteristics, contrarily to the microcystic ones, which have an infiltrating pattern and are much more progressive in their evolution.

Surgery and sclerotherapy represent the therapeutic standard of macrocystic LMs, but there is still no definitive evidence regarding which one of the two options should be considered as the first choice.

In particular, there are no specific guidelines in this regard and the literature has not yet demonstrated the superiority of one method over the other.[29]

In the absence of symptoms, developmental and functional problems, the therapeutic treatment can be deferred after the age of two. And if the symptoms remain absent or minimal, it is justified to continue clinical surveillance with therapeutic abstention, preferably associating the MRI re-evaluation (without contrast) to ascertain the volumetric stability of the lesion. However, this orientation is not shared by some authors, who consider early therapy indicated even in the presence of asymptomaticity, in consideration of the high risk of progressiveness of these malformations.[12]

In the case of symptomatic and / or developmental lesions, there are no guidelines and the standard therapeutic approach is based on sclerotherapy and excisional surgery, sometimes combined.

Surgery

According to some authors, surgery is reserved for microcystic forms, while sclerotherapy should preferably be reserved for macrocystic LMs. This indication is supported by the difficulty of carrying out effective sclerotherapy in microcystic forms and by their greater progressiveness. According to others, surgery is the first-choice option for macrocystic cervical LMs, especially in pediatric age.[11]

In all cases, patients should always be referred to a multidisciplinary facility and entrusted to a surgeon who is familiar with this type of injury and who therefore knows how to remove these malformations without damaging vital structures.[11]

The complications of surgery are: lymphorrhoea with postoperative lymphatic collections (seroma), chylothorax, infections, bleeding, transient or permanent neurological damage (more frequently it is recurrent phrenic, vagus and laryngeal nerve lesions), Horner's syndrome.[27, 30]

Regarding the long-term outcome, the incidence of relapses is high and generally sustained by incomplete exeresis, so the importance of an excision as radical as possible must be emphasized.[29]

The sites with high functional risk and morbidity are the neck, thorax (mediastinum) and orbital regions, whose specific problems are highlighted in chapter 5 (see "Locations at risk").

Sclerotherapy

Sclerotherapy is a procedure that must be performed by direct ultrasound-guided puncture under general anesthesia. Phlebographic control is generally not necessary. Only in small cystic malformations of the adult the sclerotherapy can be performed while the patient is awake. The intracystic fluid must be removed, at least partially before injecting the sclerosing agent.[3]

Single-chamber forms are those that most benefit from sclerotherapy.

The sclerosing agents used are: OK 432 (picibanil), ethanol, bleomycin, pingyangmicin (also known as bleomycin A5), doxycycline, tetracyclines, polydocanol, sodium tetradecyl sulfate.[30]

The sclerosing agent type to be chosen is based on the experience of the Center and of the operator; the choice is strictly operator-dependent.

The most severe complications are caused by the use of alcohol as a sclerosing agent; the major damages concern the skin, mucous membranes and peripheral nerves; special training in the use of alcohol is recommended in order to minimize morbidity.

The relapse or partial result is the major problem of sclerotherapy in the long term, while in the short and medium term the results are generally favorable. The procedure can be repeated.

Sclerotherapy and surgery can be used in a combined or sequential manner in the treatment of LMs.[33, 34]

In a systematic review and meta-analysis published inuary 2020 concerning 726 cases of head and neck LMs treated with sclerotherapy, complete cure (resolution of symptoms and negative clinical examination) was reported in 53% of macrocystic LM cases compared to 35% of the microcystic ones and 31% of the mixed ones.[4]

In a systematic review and meta-analysis published inust 2019 concerning 154 cases of LM of the orbit treated with sclerotherapy, a complete cure of the lesion was reported in 54.9% of cases, a low incidence of complications with a permanent outcome (2.7-3.4%) and a high incidence of temporary complications equal to 58.5%.[35]

INTERPRETATION OF THE DATA

To answer question 6, the following scientific studies were analyzed: two systematic reviews with meta-analyzes,[4, 35] four narrative reviews,[11, 30, 32, 34] two case series [29, 33] and one consensus.[31]

From the studies it emerges that in macrocystic LMs the therapeutic standard is represented by excisional surgery and ultrasound-guided sclerotherapy, but there is still no definitive evidence about the superiority of one method over the other and about which one of the two therapeutic options should be considered as the first choice.

The recent trend seems to prefer sclerotherapy, thus being an effective, repeatable procedure with a lower risk of complications or adverse events. Nevertheless, the overall risk-benefit balance of both procedures does not allow a definitive judgment, and they have not yet been formulated definitive protocols about the best therapeutic strategy based on the age of the patient and the site of the lesion.

The experience of the multidisciplinary center of reference and in particular of the operator (surgeon and interventional radiologist) play an essential role in the therapeuticision, and these are elements that can also affect the acceptability of the therapeutic procedure by the patient or parents. The quality of the evidence of the two systematic reviews with meta-analyzes, assessed through the Checklists, was found to be good.

The conclusions of the studies were consistent and without conflict, even if they did not allow to establish the superiority of one therapeutic procedure over the other.

Recommendations

The choice of therapeutic strategy, surgery or sclerotherapy must be based on a multidisciplinary approach and on an accurate overall assessment of the individual case (age of the patient, site of the lesion, risks and benefits of the therapeutic procedure).

Recommendation of Good Clinical Practice, based on the experience of the panel

Choice of the sclerosant agent

Question 7

What is the sclerosing agent of first choice for sclerotherapy in patients with macrocystic lymphatic malformation?

Traditionally the sclerosing agents used are sodium-tetradecyl-sulfate, OK-432, ethanol, doxycycline, bleomycin and pingyangmicin (also known as bleomycin A5).

Among the recently introduced drugs, the one that is receiving growing support is bleomycin, a cytotoxic antibiotic with an antitumor effect, which also exploits the sclerosing effect. The drug has the advantage of causing fewer inflammatory reactions, with consequent reduced local edema, while maintaining a high and no less sclerosing ef-

fect than the other drugs used; this aspect makes bleomycin particularly suitable in confined spaces such as the orbit.

Bleomycin is widely used both in macrocystic forms and in mixed and microcystic forms, with partial benefit percentages exceeding 90% and full benefit with total resolution of the lesion in 60% of cases.[25, 36]

The maximum recommended dose for each session is 0.5 mg/kg, with a maximum cumulative dose of 5 mg/kg.[34] The suggested time interval between one session and another is very variable, from a minimum of 4 weeks to six months.

Bleomycin acts on the endothelial cells of lymphatic cysts with a sclerosing effect mediated by the inhibition of DNA synthesis.

Side effects are: flu-like symptoms, transient hair loss and skin hyperpigmentation, to which is added the late risk of pulmonary fibrosis. The possibility that bleomycin can cause lung damage (late pulmonary fibrosis) has been known since the 1960s, but at the moment no pulmonary complications have been reported after sclerotherapy at a follow-up of less than 5 years. It should be borne in mind that bleomycin lung damage appears to occur over a longer period of time and with higher dosages than those used for sclerotherapy.[36, 37]

Doxycycline is another broad-spectrum antibiotic used as a sclerosing agent (tetracycline class) inhibitor of matrix metalloproteinases (MMPs) and vascular endothelial growth factors known as VEGF ("vascular endothelial growth factor"). The drug is well tolerated even at high doses, inexpensive and very effective in microcystic forms, and therefore indicated in extended LMs. It also has a low incidence of complications; among these, the risk of tooth staining should be noted.[38]

Pingyangmicin (Bleomycin A5) has a similar structure to standard bleomycin, and it is used in China.

The use of polydocanol in foam has been reported as a safe and effective treatment in both macro and microcystic forms, with excellent and good results respectively in 47% and 41% of cases, and a very low incidence of procedural complications. The use of this drug is however limited for cystic LMs.[39, 40]

In a systematic review with meta-analysis published inuary 2020 concerning 726 cases of LM of the head and neck treated with sclerotherapy, the total or partial benefit was over 80%, with the best results for macrocystic forms.

The sclerosing agent that had the best overall effect was doxycycline (64.3%) compared to alcohol, bleomycin, OK-432 and ethanolamine.

Doxycycline showed the best results, but also the highest complications incidence.

Morbidity (peripheral neurological damage) was 1.2%, and local complications occurred in 14% of cases.

In general, this review has shown that the results of sclerotherapy are different depending on the sclerosing agent used.[4]

In another recent systematic review with meta-analysis on a case series of 1325 cases of micro- and/or macrocystic LMs treated with sclerotherapy using different agents, it was instead concluded that bleomycin is the sclerosing agent of first choice, since an equal efficacy is associated with a low level of adverse events.[37]

The choice of bleomycin was not so much linked to efficacy, which seems to be comparable to other sclerosing agents, but to the low incidence of complications, especially when compared with ethanol.

In conclusion, it can be stated that in the literature the superiority of a sclerosing agent over the others in terms of efficacy and safety has not yet been documented, and results and complications are different depending on the drugs used. The only exception is the use of bleomycin in restricted regions and areas at functional risk, in which the edema effect of the therapy has to be limited.[37, 38, 41]

The highest incidence of complications is related to the use of ethanol (skin necrosis and neurological damage), so the use of ethanol in cervicofacial localizations is not recommended.[37]

INTERPRETATION OF THE DATA

Overall, the results of the various sclerosing agents are inhomogeneous, both in terms of efficacy and side effects and risks. To answer Question 7, six studies were identified, including two systematic reviews with meta-analyzes,[4, 37] one systematic review,[41] two narrative reviews [38, 40] and a series of clinical cases.[36]

Among the various sclerosing agents, the studies analyzed point towards a greater use of bleomycin, which demonstrates good efficacy and a low level of adverse events. However, the drug cannot be considered as the first choice sclerosing agent, with the sole exception of the restricted sites where its low edema effect must be exploited (*e.g.* orbital region). The studies agreed that bleomycin is the agent of choice only in the orbital region.

In all of the other cases, the experience of the multidisciplinary center and good clinical practice are the essential elements in choosing the sclerosing agent. The conclusions of the studies appear consistent and conflict-free; the quality of the evidence of the two systematic reviews with meta-analysis, assessed through the Checklists, was found to be good.

Recommendation

1. The choice of the sclerosing agent is linked both to the site of the malformation and to the experience of the operator.

Recommendation of Good Clinical Practice, based on the experience of the panel

2. The drug of choice in LM (macro-micro-cystic) localized in restricted areas and at risk of functional damage is bleomycin.

Strong recommendation in favor, level of evidence 1-

Extra-truncular (or common) lymphatic malformations of the microcystic type

Clinical aspects

Question 8

What are the clinical manifestations at the onset (first diagnosis or clinical suspicion) of microcystic lymphatic malformation?

Microcystic LMs have infiltrating characteristics; the regions most frequently involved are the face, the neck and the thorax.

The most frequent site is the superficial one (skin, mucous membranes of the oral cavity, tongue, genital region, conjunctivae), where the lesions have the appearance of vesicles, which ooze and bleed, inducing maceration, aesthetic impairment, scars, pain, bacterial infections, impaired quality of life and sometimes anemia. In addition to this general clinical picture, functional complications related to the site of the malformation are added. History progressively worsens during life (progressive increase in the number of injuries and related complications).

At the skin level, microcystic LMs are more often complicated by bacterial infections, often difficult to eradicate and whose treatment is symptomatic (antibiotics and corticosteroids) to limit or eradicate the acute event, which can then be followed by specific therapies. When they are located deeper (subcutaneously, retroperitoneum, mediastinum, neck), they can become responsible for soft tissue hypertrophy and asymmetries.[1, 2]

The mucosal and lingual localizations of the oral cavity can cause oral bleeding, hypersalivation, macroglossia, hypertrophy of the floor of the mouth, difficulty in swallowing, difficulty in speech, dental malocclusion, facial asymmetry, breathing problems.[1]

Bone localizations are very rare.

They are on the whole developmental and infiltrating lesions.

No possibility of prenatal diagnosis.

INTERPRETATION OF THE DATA

To answer Question 8, 2 clinical studies were considered (a guideline and a narrative review) already reported in the chapter on macrocystic lymphatic malformations, as these are studies that analyze both micro- and macro-cystic forms, as these are often associated.

Micro-cystic LMs more frequently have a superficial localization, involving the skin and mucous membranes, so the clinical diagnosis is easy in most cases.

Recommendations

The presence of small vesicles of skin and mucous membranes that ooze, bleed, macerate and become infected, must orient towards the diagnosis of microcystic lymphatic malformation. Since these malformations are progressive, early diagnosis plays an important role for therapeutic purposes.

Recommendation of Good Clinical Practice, based on the experience of the panel

Instrumental diagnosis

Question 9

What are the instrumental investigations to be carried out for the confirmation of the clinical diagnosis of microcystic LM and for the assessment of extension in anticipation of therapy?

The first investigation to be carried out to confirm the clinical diagnosis is the echo-color-Doppler investigation, which demonstrates that the region of the malformation has a heterogeneous appearance, with iso- and hypo-echogenic tissue, with the appreciation of numerous small subcentimetric cysts with liquid content in the context of the lesion, most frequently scattered in the subcutaneous and submucosal connective tissue without evidence of cleavage planes.

MRI represents the second level investigation, which follows the ultrasound evaluation and allows to define the extent of the lesions, which often lead to occupy the peripharyngeal and laryngeal spaces, the mediastinum and the retroperitoneum.

In general, MRI is particularly useful for the extension budget, but it should be noted that microcystic forms are difficult to recognize with MRI, even after injection of contrast medium; the differential diagnosis arises above all with venous malformations.

The monitoring of the evolution of these malformations should preferably be performed with ultrasound, suggesting re-evaluation with MRI in case of clinical and ultrasound evidence of worsening of the lesion.[1]

INTERPRETATION OF THE DATA

The clinical picture of microcystic LMs must be completed with instrumental investigations, in order to allow a balance of the extension of the lesions and to allow the monitoring of evolution.

There are no adequate studies to evaluate the scientific evidence of the role of ultrasound and MRI in the diagnosis of micro-cystic LMs, and there are no operational protocols for the instrumental control of these lesions over time.

Recommendations

The clinical picture must be confirmed and supported by instrumental investigations (ultrasound and MRI) to assess the extent of the lesion, especially in the suspicion of deep localizations associated with cutaneous and mucosal ones.

Recommendation of Good Clinical Practice, based on the experience of the panel

Therapy

Question 10

What are the therapeutic procedures indicated in microcystic lymphatic malformations?

There are no guidelines for the management of microcystic LM, and there are several therapeutic options: sclerotherapy, laser therapy, radiofrequency ablation, surgery and drug therapy.

None of these therapeutic procedures can be considered a resolutive therapy and superior to the others, and the tendency is to use them in variously combined strategies depending on site and clinical problems.

Considering the difficulty or impossibility of sclerotherapy for the small size of the cysts, many authors consider surgery as the first therapeutic option choice, while taking into account the impossibility of radical excision due to the infiltrating nature of these anomalies, and therefore the high risk of relapses.

The laser is widely used in superficial, cutaneous and mucosal forms, but there is no lack of indications for deeper sites (interstitial laser, endovascular laser).

Radiofrequency ablation is very little used.

Drug therapy is still off-label, used for compassionate purposes or, in any case, where all other (invasive) therapies have failed (see "Pharmacological Treatment").

The effectiveness of all available therapies taken individually is partial, incomplete and transient, with a very high relapse rate, so a multidisciplinary management is required in most cases.[29]

Surgery

According to some authors, surgery is reserved for microcystic forms, while sclerotherapy should preferably be reserved for macrocystic LMs. This indication is supported by the difficulty of carrying out effective sclerotherapy in microcystic forms and by their greater progressiveness.

In all cases, patients should always be referred to a multidisciplinary facility and referred to a surgeon who is familiar with this type of injury.[11]

The possibility of radical excision of the microcystic forms is generally very low, and the risk of recurrence is high. Surgery associated with or followed by bleomycin sclerotherapy is a recently introduced technique to reduce the recurrence risk, but its results need confirmation.[2, 33, 42]

The most frequent site of micro-cystic LM is the cervico-facial one. Here the malformation is most often localized superior to the level of the mylohyoid muscle and tends to infiltrate the oral cavity, oropharynx, tongue, parotid, submandibular gland, supraepiglottic area, parapharyngeal and retropharyngeal spaces. Consequently, radical excision of these lesions is rarely possible.

For surgery in cervico-facial localizations, mapping of the facial nerve and continuous electromyographic monitoring are indispensable intraoperatively. In other locations, the surgery of superficial forms involves the removal of portions of skin and subcutis infiltrated by the malformation, for which the use of skin grafts, rotation flaps and skin expanders be necessary.

In deep localizations and in cases of tissue hypertrophy, excisional surgery is indicated for the reduction of the lesion volume.

In the case of facial asymmetries with consequent serious psycho-social problems of the patient, surgery must be proposed with great caution, specifying to the patient that there are no certain guarantees of results, in the face of high risks of morbidity and also potential risks of worsening.

The major complications of surgery are: lymphorrhoea with postoperative lymphatic collections (seroma), transient or permanent neurological damage (most frequently recurrent phrenic, vagus and laryngeal nerves), Horner's

syndrome, difficulty in healing surgical wounds with the formation of keloids, infections, early relapse.

The sites with high functional and morbidity risk are neck, thorax (mediastinum) and orbital region, whose specific problems are highlighted in chapter 5 (see "Locations at risk").

Sclerotherapy

Il farmaco maggiormente utilizzato è la bleomicina, in quanto poco edemigena e priva di neurotossicità, per cui si può utilizzare nelle lesioni adiacenti al nervo facciale e per quelle dell'orbita.[2, 35, 43]

The most widely used drug is bleomycin, as it has little edema and no neurotoxicity, so it can be used in lesions adjacent to the facial nerve and for those of the orbit.[2, 35, 43]

For superficial lesions of the tongue, mucous membranes and skin, bleomycin seems to work very well; it can be injected directly into the lymphatic vesicles or into the mucosa and into the skin and subcutis adjacent to the lesions. In the localizations of the upper airways, bleomycin can be used in combination with a CO2 laser.[2]

Bleomycin sclerotherapy is also indicated in macroglossia sustained by microcystic LM; it allows good results with the possibility of normalization of the lingual volume and disappearance of intraoral mucosal vesicles. Therapeutic sessions are recommended every 4-6 weeks with a drug dosage of 0.2 mg/kg (0.75-1 U/kg per session) and cumulative amount of bleomycin less than 15 U/kg.[36]

In the localizations of the oral cavity, macroglossia and involvement of the floor of the mouth can be the cause of glossoptosis, a condition that causes deformity, altered buccal opening, difficulty in chewing and speaking. In such situations, it is indicated a combined therapy of an off-label medical therapy (rapamycin) associated with sclerotherapy (bleomycin) and surgical reduction of the tongue or the thickness of the floor of the mouth. The procedure should be done at an early age, as late treatments impair jaw development and dentition.[2] Parents should always be well informed about the risks of failure and morbidity of the procedure.

Other sclerosing agents used are: OK 432, polidocanol, alcohol, doxycycline, ethanolamine. Doxycycline had the best results but also the highest incidence of complications.[4]

A new technique has recently been introduced for microcystic lesions ("lymphography -like technique"), which involves the insertion of multiple small needles into the malformation, with subsequent slow infusion of the sclerosing agent.[4]

Ablation with radio frequency

This technique is used in some Centers for microcystic LM of the oral cavity. In the literature, the major series includes 26 cases. The treatment appears to be effective and well tolerated, with rapid resumption of nutrition and minimal complications.

The principle is that of the destruction of the pathological tissue at low temperatures, for which thermal injuries to the surrounding tissues are rare. Ablation can be carried out at high frequencies for deeper tissues (below the mucosa), or at low frequencies for more superficial lesions, along with continuous saline irrigation. The procedure should be performed under anesthesia and intubation.

The most common indications for this therapy are small but recurrent superficial bleeding and infections that are not very responsive to antibiotics.

In conclusion, radiofrequency represents a valid option to laser therapy for lymphatic vesicles of the oral cavity, but experiences are very limited.[44]

Laser therapy

The CO2 laser and the Neodymium YAG laser (neodymium-yttrium-aluminum-garnet laser) allow the best results; the latter can be superficial or endolesional. The Nd: YAG laser is the most effective in the treatment of superficial microcystic forms of skin and mucous membranes. The CO2 laser allowed satisfactory results in malformative localizations of the oral cavity.

Pulsed dye laser and diode laser are less used.

The most frequent adverse outcomes are scarring and local recurrence.

The CO2 laser non-selectively vaporizes the superficial vesicles and seals the lymphatic channels, but it rarely allows definitive results, while improving the symptoms; the disadvantages of this method include the need for local or general anesthesia and side effects such as persistent erythema, permanent hypopigmentations and scar retractions.

The 1064 nm wavelength Nd: Yag laser acts more selectively, causing photocoagulation of the small skin vesicles, but it can have the same drawbacks as the CO2 laser (scars and relapses).

The same intralesional laser can be used for microcystic LM of the oral cavity, tongue and supraglottic airway, even in patients under one year of life. Intralesional lasers include two categories: those specific for hemoglobin (hemoglobin-specific laser wavelenghts, HSLWs) and those specific for liquids (water-specific laser wavelenghts, WSLWs).

WSLWS lasers target lymphatic fluid and, among them, 1064-, 1320-, and 1470-nm lasers are capable of producing thermal damage within lymphatic cysts, as they are absorbed by fluid and collagen, resulting in contraction of the cystic walls.[45]

The goal of intralesional laser therapy is the reduction of volume and the extension of the malformation; the treatments are multiple and allow favorable results in the majority of cases, even if transient.

The diode laser with a wavelength of 808 nm was used in the treatment of superficial microcystic LM of the tongue with an ablative effect, but with scarring fibrosis.

The pulsed dye laser at 595 nm is used for the treatment of superficial microcystic LM with pink-red vesicles of 1-4 mm in diameter (*i.e.* with blood component); this also has a positive effect in some cases from a cosmetic point of view, being devoid of significant side effects; the treatment can therefore be repeated. Relapses are frequent, because it acts only on very superficial lesions.

Laser therapy can be used in combination with other therapeutic options (surgery, sclerotherapy, radiofrequency ablation, drug therapy).

It is crucial to minimize the thermal effect of the laser on the structures surrounding the LM or infiltrated by it, using irrigation with cold water and frozen compresses.

Early complications of the laser include: superficial skin burns, infections, scars, ulcerations, bleeding, transient neurological (facial nerve) damage.

The laser therapy sessions can be repeated every 3-6 months.

INTERPRETATION OF THE DATA

In microcystic LMs there is no therapeutic standard, but several options that can also be used in combination.

Several recent articles report favorable results with surgery, sclerotherapy, laser and radiofrequency, but the case histories are limited. There are only two significant scientific systematic reviews with meta-analyzes on significant case histories (of 726 and 154 patients, respectively), which have recently reported the outcomes of sclerotherapy in macro- and micro-cystic lymphatic malformations, but without allowing any definitive conclusions, nor the definition of a protocol. Furthermore, the parameters used and the data reported are very heterogeneous and difficult to compare, especially because the results are often incomplete.

Eight clinical trials were analyzed to address this issue: two systematic reviews with meta-analyzes,[4, 35] two narrative reviews,[2, 44] and four case series.[33, 36, 43, 45]

From these studies it emerges that there is no evidence of superiority of one method over the other, both therapeutic and to manage the evolution of the disease, and no therapeutic option can be considered of first choice. The combined therapeutic treatment allows the best results, even if only partial and/or temporary.

Recommendations

In microcystic LM there is no first choice therapeutic option. The best treatment is based on the variable combination of four therapeutic practices (surgery, sclerotherapy, laser and radiofrequency).

Recommendation of Good Clinical Practice, based on the experience of the panel

Pharmacological treatment

Question 11

What are the possibilities of pharmacological treatment in microcystic and mixed (micro-macro-cystic) lymphatic malformations?

In cases of microcystic or mixed, symptomatic and developmental LM, refractory to standard therapies, off-label drug therapy is indicated. The drug that is providing the best results, not only for LM, but for all low-flow vascular malformations, is rapamycin (sirolimus). The first article on the favorable outcome of sirolimus as an antiangiogenic drug was published in 2011.

It is a macrolide antibiotic born as an antifungal drug and subsequently used as an immunosuppressant in kidney transplants in pediatric age.

It acts as an inhibitor of the mTOR factor (mammarian target of rapamycin), which in turn activates protein synthesis and angiogenesis. In addition, sirolimus blocks VEGF (vascular endothelial growth factor) and prevents the "hypoxia-inducible factor-1" which stimulates angiogenesis.

The standard dosage of oral sirolimus to start the therapy is 0.8 mg/m^2 twice a day in children and 0.05 mg/m^2 twice a day in adults.[46-49]

Dosages can then be varied to maintain drug blood levels between 5 and 10 nanograms/mL.[48] According to some, the therapeutic range can fluctuate between 10 and 15 ng/mL.

In superficial skin malformations, rapamycin can also be used topically.

In a recent systematic review, including 2 randomized controlled trials and 2 prospective non-randomized stud-

ies, the outcomes of 317 cases of patients with vascular abnormalities (including 108 lymphatic malformations) treated with oral sirolimus and 56 cases treated with topical sirolimus were analyzed.

In LMs (108 cases) there was an improvement in 95% of treated cases, with a non-specific reduction in the volume of the malformation in 77.8% of cases.[51]

The most frequent side effects of oral sirolimus are: stomatitis, dyslipidemia (hypertriglyceridemia and hypercholesterolemia), infections, bonerow inhibition with leukopenia and thrombocytopenia, gastrointestinal symptoms, eczema.

A major concern relates to the risk of infection with Pneumocysts carinii pneumonia; for this reason, preventive treatment with trimethoprim-sulfamethoxazole is recommended for the entire duration of therapy.

In a series of 50 pediatric patients there was a favorable (complete or partial) response to rapamycin in 89.3% of cases, with few and well tolerated side effects.[46]

Complete response means total (clinical and radiological) disappearance of the malformation and symptoms; partial response means improvement >20%.

In thoracic, abdominal and visceral locations in general, the effectiveness of sirolimus is more limited than in cervico-facial locations.

There is currently no consensus on the optimal dosage and duration of treatment for oral sirolimus.[51]

Rapamycin administered orally is also effective in the neonatal period, and can be used in LMs that compress and divert the airways, with the aim of reducing the need for tracheotomy.[50]

Unfortunately, the information available on efficacy and side effects in the newborn is still very scarce.

Even in the newborn, the initial dosage is 0.8 mg/m^2 twice a day, and then blood levels are maintained between 4 and 12 ng/mL. However, some prefer to use half of the starting dosage.

The average duration of therapy is 12 months for all ages.[50, 52]

The following are under construction:

• a prospective multicenter open study (called SILA) to assert the efficacy and safety of rapamycin in complex LM refractory to standard therapies;[53]

• a single-center prospective phase II study with patients with low-flow vascular malformations refractory to standard therapy and treated with sirolimus for a median of 12 months;[48]

• a phase 2 randomized observational French multicenter study recruiting 50 patients aged 6 to 18 with large and complicated low-flow vascular malformations. The aim of the study is to resolve the current uncertainties related to the efficacy of sirolimus in reducing the volume and extent of malformations. The project highlights the current lack of guidelines and clinical trials and highlights the discrepancy between the modest reduction in volume (assessed with MRI) and the significant improvement in symptoms during therapy.[54]

Overall, oral sirolimus is an effective and safe therapy, capable of reducing symptoms and improving the quality of life in most cases.[48, 50]

Despite the evidence of clinical improvement, MRI shows a significant reduction in the volume of the malformation only in a minority of cases.[48]

Another drug used in LM refractory to standard therapies is sildenafil, but its antiangiogenic effect is still under investigation. In general, the drug is not convincing and its use is not encouraged.

Sirolimus is also used topically for the treatment of superficial lymphatic vesicles of the skin, with the aim of reducing local symptoms and the incidence of inflammatory-infectious skin complications.[51, 55, 56] Currently the results with topical sirolimus in skin localizations are however scarce and conflicting.

INTERPRETATION OF THE DATA: SYSTEMIC RAPAMYCIN (ORAL)

To answer Question 11, we analyzed the following scientific studies: three systematic reviews,[47, 49, 51] three series of clinical cases[46, 50, 52] and the protocols related to three trials in progress, two of which are not yet completed: a single-arm prospective multicenter trial,[53] a phase II prospective study[48] and a phase II multicenter trial.[54]

Overall, the results of off-label drug therapy and their definition are very inhomogeneous, especially because different terminologies and descriptions are used. A systematic comparison of the results was not possible.

In most of the articles, an exact and/or homogeneous response to sirolimus therapy is not reported, but terms such as “marked improvement,” “significant volume reduction,” “significantrease,” “partial response,” etc. are used. Therefore the results are not comparable, besides the fact that the number of reported cases is always modest. In general, we can say that the majority of patients have a partial response and a partial benefit in terms of symptoms and quality of life.

Therefore, the primary objective of drug therapy is to control the symptoms and progression of the disease, to maintain functionality and to preserve the best possible aesthetic appearance; but there is a low level of evidence

that sirolimus can modify the prognosis of these anomalies.

Duration of therapy and dosage also differ in the reported cases, since there are no guidelines here either, and this is especially true for children and infants.

The low level of the methodology used in the majority of the studies, the lack of randomized controlled trials and concluded, the heterogeneity in the definition of the outcomes of the therapy, the poor definition of the toxicity risk should also be noted.

Recommendations systemic rapamycin (oral)

1. Off-label drug therapy with rapamycin is recommended in cases of symptomatic, progressive and refractory cystic lymphatic malformations to conventional therapies.
Recommendation of Good Clinical Practice, based on the experience of the panel

2. The initial dose of therapy is 0.8 mg/m^2 twice a day, with the aim of maintaining plasma levels of rapamycin in the 5-15 ng/mL range.
Recommendation of Good Clinical Practice, based on the experience of the panel

3. In the absence of guidelines and uniform protocols, a duration of therapy of 12 months is recommended, with periodic clinical, haematological and instrumental checks.
Recommendation of Good Clinical Practice, based on the experience of the panel

INTERPRETATION OF THE DATA: TOPICAL RAPAMYCIN (SIROLIMUS)

Three recent clinical studies related to the use of topical sirolimus in the treatment of superficial micro-cystic lymphatic malformations were analyzed: a series of cases,[55] a systematic review,[51] a multicenter clinical trial in phase II.[56]

The methods of use of topical sirolimus are very heterogeneous and the results are difficult to define, and a comparison between them is not possible. The duration of therapy is also uneven and ill-defined.

Overall, there is a low level of evidence regarding the usefulness of topical sirolimus in skin microcystic lymphatic malformations.

Recommendations Topical rapamycin (sirolimus)

1. The use of topical sirolimus represents an off-label therapy that is indicated in microcystic LMs of the skin to reduce exudates, bleeding and vesicles, skin thickening, pain and itching, cosmetic problems.
Recommendation of Good Clinical Practice, based on the experience of the panel

2. You can use the cream or the liquid solution, but it is preferable to use the cream with concentrations in the range 0.015% -8% (most used dosage 0.1%).
Recommendation of Good Clinical Practice, based on the experience of the panel

Risky localizations

LM cervico-mediastinics with compression and obstruction of the airways. indications for tracheotomy

Question 12

What is the correct therapeutic management of cervico-mediastinal cystic lymphatic malformations with compression and obstruction of the airways?

In macrocystic or mixed cervical ML with evidence of obstruction of the laryngotracheal airway, the need for tracheostomy should be assessed when the lesion is in contact with the airway and surrounds it for more than 50% of the circumference, regardless of the macro- or micro-cystic nature of the lesion. MRI is able to provide predictive parameters of the need for tracheostomy, evaluating the extent of contact between the malformation and the laryngotracheal axis. The extent of this contact should be monitored.[26, 57]

If sclerotherapy is indicated, tracheostomy becomes highly advisable, although there are sporadic reports in the literature of sequential sclerotherapy sessions performed without tracheostomy.[20]

On the other hand, if it is opted for surgery and a total or subtotal excision of the malformation is expected, the tracheotomy is not necessary (and if already present, it can be removed before discharge if the surgery has been successful).

For cervical locations, surgical access is preferably anterolateral cervical along the anterior edge of the sternocleidomastoid), associated with median sternotomy in the case of cervico-mediastinal LM.

Mediastinal LMs are more often of the infiltrating type (microcystic or mixed), located in the upper and anterior mediastinum and in most cases are not responsible for airway obstruction. It should be reiterated that, whatever the site, MRI provides predictive parameters for the need for tracheostomy.[27, 58]

In the rare cases of mediastinal cystic LMs complicated by tracheal compression and obstruction, tracheotomy becomes useless, sclerotherapy is not indicated and excisional surgery becomes the only option; in these cases, surgery is recommended through a median sternotomy, possibly followed by irrigation of the operative field with a sclerosing agent (bleomycin).[59]

On the other hand, if the tracheal obstruction is proximal, sclerotherapy can be performed, but it requires tracheotomy, in order to avoid long periods of intubation and stay in intensive care, as the postprocedural edema is of an unpredictable extent and duration.[59]

In the case of asymptomaticity or mild symptoms, with instrumental evidence (MRI) of the absence of airway obstruction, a conservative strategy and clinical-instrumental follow-up are recommended.

In conclusion: in the mediastinal area, sclerotherapy should be considered a high-risk procedure, while surgery can be performed with a low incidence of complications and good results, as long as it is in expert hands and in a multidisciplinary perspective.[59]

Complications of surgery are: chylothorax, recurrent phrenic, vagus and laryngeal nerve injuries, bleeding and infections.

Medical antiangiogenic therapy with rapamycin can be used in combination with surgery or sclerotherapy already in the newborn, in order to reduce the volume of the lesion and therefore the need for tracheotomy (see "Pharmacological treatment").

A dosage of 0.8 mg/m^2 twice daily can be started, then dose adjusted to maintain a blood level >4 nanograms/mL (recommended level between 4 and 12 ng/mL).[52, 60]

In the case of prenatal diagnosis, if there is evidence or well-founded suspicion of airway obstruction with respiratory distress at birth, tracheostomy should be planned and should be part of an ex-utero intrapartum treatment (EXIT) program.[26]

Tracheostomy at a very early age involves delay in language development, even when it is only temporary; the age of the child at the time of the tracheotomy and its duration are crucial. To date, there are no shared specific indicators for tracheostomy in young children.[26]

In all cases, patients should always be referred to a multidisciplinary structure and entrusted to a surgeon who is familiar with this type of injury and with the complex anatomy of the neck and mediastinum, and who therefore knows how to remove these malformations without damage to vital structures.[11]

INTERPRETATION OF THE DATA

To answer question number 12, considering the rarity of these anomalies, all recent articles have been analyzed in detail which, taken as a whole, have allowed an exhaustive answer; there are four narrative reviews[11, 26, 27, 59] and two case series.[52, 60]

In particular, it is clear that in macrocystic or mixed cervical and cervico-mediastinal lymphatic malformations with obstruction of the laryngotracheal airway, it is crucial to ensure ventilatory assistance in anticipation of therapeutic procedures.

For these patients, mostly pediatric, the focus of the discussion concerns the assessment of the need for tracheostomy; only afterwards elective therapy can be programmed (surgery and/or sclerotherapy).

The decision regarding the tracheotomy must always be defined, and the transient tracheotomy must be considered an indispensable procedure in cases at risk, regardless of the patient's age.

The excisional surgery of these malformations involves a long and complex operation, burdened by the risk of high morbidity; for this reason these cases should be dealt with in highly specialized centers, and the surgeon must be familiar with this type of injury. The quality of the evidence was assessed through the Checklist and was rated as good overall.

The studies considered are relevant to the target population, the conclusions are consistent but there is a potential risk of bias, especially in consideration of the limited series.

Finally, the favorable effect of drug therapy with rapamycin in association with invasive therapies should be noted, for which reference is made to "Pharmacological treatment."

Recommendations

1. It is recommended to always perform MRI, before any treatment, to assess whether and to what extent the lesion is in contact with the airway, as MRI is able to provide predictive parameters of the need for tracheostomy.
Strong recommendation in favor, level of evidence 3-4

2. In the case of contact between the malformation and the laryngotracheal axis, the extent of this contact and its location must be monitored.
Recommendation of Good Clinical Practice, based on the experience of the panel

3. In macrocystic or mixed cervical LMs with evidence of obstruction of the laryngotracheal airway, it is recommended to always evaluate the need for tracheostomy before any invasive therapeutic action.
Strong recommendation in favor, level of evidence 3-4

ML of the orbit

Question 13

What are the therapeutic options in cystic (macro-, micro-, mixed) lymphatic malformations of the orbital region?

LMs of the orbit clinically present in the firstade of life with ptosis, proptosis, restriction of ocular motility, diplopia, scotoma, optic nerve compression, aesthetic damage, pain, bruising and local hemorrhages.

Early therapeutic treatment is crucial to prevent vision damage and it includes sclerotherapy, surgery and drug-therapy. There is still no standard treatment goal and there are no randomized controlled trials for the treatment of cystic LM of the orbit in children and young adults.[61]

A recent systematic review showed no significant differences in outcome between surgery and sclerotherapy, pointing out that the two techniques can also coexist. In other words, there is still no definitive consensus on the optimal therapeutic treatment of orbital LMs.[39, 63, 64, 66]

The complex anatomy of the orbit and the fact that its contents can easily suffer from a compartment syndrome explain the difficulties of treatment with a favorable outcome.[65]

Sclerotherapy is the first-choice therapeutic option in the limited series of the lastade, and bleomycin is the most frequently used sclerosing agent.[35, 66, 67, 68]

The drug has the advantage of causing fewer inflammatory reactions, with consequent reduced local edema, while maintaining a high and no less sclerosing effect than other drugs; this aspect makes it particularly suitable in confined spaces such as the orbit.

The maximum recommended dose of bleomycin for an orbital LM is of 1U/kg per session, with a maximum cumulative dose of 15U per session and a maximum cumulative dose of 150U for all sessions; there has to be a minimum interval of 6-8 weeks between one session and the following.[69]

In a systematic review and meta-analysis published inust 2019 concerning 154 cases of LMs of the orbit treated with sclerotherapy, complete wound care was reported in 54.9% of cases and a need for emergency postsclerotherapyompression surgery 3.4%.

Complications of sclerotherapy were: loss of vision (1 case, 2.7%); compartment syndrome (8 cases, 3.4%); local sensitivity defects (1 case, 2.7%) temporary complications (edema, pain) in 71 cases (58.5%), skin necrosis (1 case, 2.7%).

Ethanol carries the greatest risk of complications for this site, while bleomycin had the lowest incidence of complications.[35]

Drug therapy with sirolimus can be used in cystic LMs of the orbit, alone or in association with invasive therapies (see "Pharmacological treatment").

INTERPRETATION OF THE DATA

Six scientific studies have been identified that together express clearly and without conflict the suggested treatment for cystic lymphatic malformations of the orbit, but with evidence of inhomogeneity of the data. They are a systematic review with meta-analysis,[35] four reviews narratives,[61, 65, 67, 69] a case series.[63]

There are still no randomized controlled trials for cystic LMs of the orbit, and there is no definitive consensus on the optimal therapy.

The difficulties of the therapeuticision are related to various factors: case studies and therefore limited experiences, complex anatomy of the orbit and the fact that the orbital content can easily suffer from compartment syndrome with loss of vision.

In recent years, bleomycin sclerotherapy seems to have become the therapeutic option of first choice, as an alternative to surgery, but the numbers of cases treated and the results, reported in an inconsistent manner, do not yet allow definitive conclusions.

The choice of therapy would still seem linked to the experience of the reference center.

Recommendations

1. In symptomatic LMs of the orbit, early therapeutic treatment is recommended to prevent damage to vision.
Strong recommendation in favor, level of evidence 1+

2. Although there is still no definitive consensus on the optimal therapeutic treatment for LM of the orbit, sclerotherapy with bleomycin is recommended as the first therapeutic option.
Weak recommendation in favor, level of evidence 1+

Intestinal and retroperitoneal LM

Question 14

What are the therapeutic indications of intestinal and retroperitoneal cystic lymphatic malformations?

Abdominal cystic lymphatic malformations are rare. They originate in the sub-peritoneal space and retroperitoneum and expand into the omentum and mesentery. The most frequent appearance is that of macrocysts, single or multichamber, with homogeneous liquid content, thinta and walls, sometimes also with hemorrhagic content and calcifications in theta.

The most frequent symptoms are: progressive abdominal distension, pain, infection, anemia.

The onset of symptoms can also be acute: acute abdo-

men, infection, bleeding, volvulus. Symptoms occur more frequently in the pediatric age.

The initial diagnosis is based on the clinical picture and ultrasound, the latter followed by MRI for diagnostic confirmation and extension budget in anticipation of therapeutic treatment.

The differential diagnosis is made against: chylous ascites, extrapancreatic necrosis, lymphocele, cystic mesothelioma, peritoneal neoplasms with cystic components with mucinous or myxoid content.[21]

Surgical options include sclerotherapy and surgery.

Small and asymptomatic LMs do not require therapy, but only an ultrasound follow-up and also MRI in selected cases.

Surgery is the prevailing option in the small cases reported, but it is burdened by a high incidence of morbidity and relapses.[70]

Sclerotherapy is today an effective alternative therapeutic measure to surgery. It is carried out under ultrasound guidance; among the agents used, doxycycline in sequential sessions allowed good results (in 8 cases a volumetric reduction of cysts was reported equal to 96.7% at ultrasound control, and 83.3% at MRI control). However, remember that the choice of the sclerosing agent is operator-dependent.[71-73]

INTERPRETATION OF THE DATA

These are rare malformations. To respond to Question no. 14 four articles were analyzed: three narrative reviews[21, 70, 72] and a series of cases.[71]

The results of surgical therapy and sclerotherapy are based on modest case studies, the data of which are inhomogeneous and difficult to compare, to which is added the fact that different or incomplete terminologies and descriptions are used.

In general, we can say that there is no first-choice therapeutic option, and both possibilities can allow good results.

Recommendations

1. In the case of abdominal symptoms in pediatric age, the possibility of abdominal LMs should always be suspected.
Recommendation of Good Clinical Practice, based on the experience of the panel

2. Cystic-type abdominal lymphatic malformations that become symptomatic must always be treated, as they are at risk of progression and complications. Surgery and sclerotherapy are currently both valid and feasible therapeutic measures.
Recommendation of Good Clinical Practice, based on the experience of the panel

Complex lymphatic malformations

Definition

The term "Complex Lymphatic Malformations" (CLM) has recently been formulated to indicate a category of rare and generally refractory LMs, which have many similar or common clinical-instrumental characteristics. This category includes the following pathologies:

- Generalized Limphatic Anomaly (GLA);
- Gorham-Stout Disease (GSD);
- Kaposiform LymphAngiomatosis (KLA);
- Central Conducting Lymphatic Anomaly (CCLA).

Question 15

What are the clinical, hematological and instrumental characteristics that allow us to make the diagnosis (or at least the clinical suspicion) of Complex Lymphatic Malformation?

Generalized lymphatic anomaly (GLA)

It is a rare lymphatic anomaly characterized by a diffuse or multicentric proliferation of dilated lymphatic vessels that have a microcystic appearance. It has a variable clinical presentation, as it can affect different districts, especially bones, soft tissues, mediastinum, lungs, liver, spleen.

The dominant element of GLA is segmental bone osteolysis, associated with proliferation of lymphatic vessels in the areas adjacent to the diseased bone. The clavicle, ribs, cervico-thoracic vertebrae and skull are more frequently involved. The most frequent localization of all is the costal one which, in most cases, is associated with chylothorax.

Osteolysis is limited to the central medullary (spongy) area of the bone, without cortical involvement, and the lesion is not progressive.

The absence of cortical osteolysis and progressivity distinguishes it from GSD, characterized by progressive osteolysis with cortical involvement, which leads to the loss of cortical bone (hence the term "phantom bone syndrome").

The soft tissues infiltration surrounding the osteolytic lesions shows a hyperintense signal in the T2-weighted MRI sequences with fat-subtraction, and intense enhancement after gadolinium administration.

The clinical picture is dominated by: pain, spontaneous fractures, chylothorax.

Kaposiform lymphangiomatosis (KLA)

Mulliken and colleagues described for the first time in 2014 a new lymphatic anomaly with a peculiar histological pattern and a poor prognosis, which they called ka-

posiform lymphangiomatosis (KLA), due to the unusual association between dilated lymphatic vessels and clusters of perivasal "spindle cells," which resemble the spindle cells of Kaposi's sarcoma.

They described 20 pediatric cases (mean age 6.5 years) characterized by a triad: respiratory symptoms, blood coagulation disorders, and palpable and mediastinal developmental masses.

Despite multimodal and aggressive therapy, they reported a 5-year survival of 51% and an overall survival of 34%, with a mean interval of 2.75 years between diagnosis and death (range 1-6.5 years).

In 2018, during the revision of the ISSVA classification, this lymphatic anomaly was included as a subtype of GLA, and is currently considered an aggressive disease with a poor prognosis.

The clinical-instrumental signs of KLA are: osteolytic lesions without cortical involvement, chylothorax, pericardial effusions, mediastinal masses, retro-peritoneal and soft tissue masses. Mortality is generally associated with progressive pulmonary disorders and hemorrhagic manifestations secondary to blood coagulation disorders.

In a recent review including a series of 20 other KLA cases, the characteristic clinical picture was confirmed: respiratory symptoms, hemorrhagic manifestations, pseudotumor-like masses, fractures. The bleeding is due to thrombocytopenia.

There is always malformative tissue at the mediastinal and hilar pulmonary levels, with a characteristic of infiltrating soft tissue thickening, or pseudo-tumor mass. This pathological picture at the posterior mediastinal level shows infiltrating characteristics and it is distributed along the intrapulmonary broncho-vascular bundles, while at the anterior mediastinal level it more often assumes the features of a mass. Pleural effusion occurs in over 60% of cases and it can be bilateral.

Both the infiltrating aspect of the pathological tissue and the pleural effusion are hyper-intense in the T2-weighted MRI sequences.

Visceral anomalies (liver and spleen) are associated in over 50% of cases (hyper-intense rounded and inhomogeneous cystic lesions in MRI images and hypoechoic ultrasonography).

Pathological tissue with an infiltrating appearance can also be present at the retroperitoneal level, with infiltration of the mesentery along the vascular bundles, hepatic hilum, renal hilum.

Bone lesions are present in 60% of cases; the most frequent site is the rachis.

A surgical biopsy, even if carried out in different sites (mediastinum, lung, thymus, pericardium, pleura, spleen, bone, subcutaneous tissue, skin), demonstrates both malformative and tumor aspects: dilated lymphatic vessels associated with small peri- and intravascular agglomerates of spindle cells, free from atypia, but with proliferative aspects.

Gorham-stout disease (GSD)

It is a rare, sporadic, CLM of unknown etiology. It manifests itself with spontaneous and sometimes massive osteolysis, associated with intraosseous vascular proliferation of small predominantly lymphatic blood vessels, with secondary osteolysis that involves progressive destruction and resorption of both spongy and cortical bone, which is replaced by fibrous tissue.

It preferably affects children and adolescents, with no difference between the sexes.

The syndrome can involve one or more bones, usually contiguous, with more frequent localization of the pelvis, shoulder girdle, spine, ribs and skull bones. Variable involvement of the adjacent soft tissues is associated, which can be infiltrated by the vascular malformation.

Chylothorax is associated in 40% of cases.

The clinical picture is characterized by pain, spontaneous fractures, chylothorax. The progression of osteolysis can stop at any time, but often evolves with the complete loss of bone tissue, which is replaced by a fibrous band; this picture suggested the term "phantom bone syndrome".

As in GLA diagnosis is difficult and is reached by exclusion (differential diagnosis with osteolysis secondary to infections, inflammation, endocrinopathies, neoplastic processes). Confirmation of diagnosis requires bone biopsy.

This is a progressive and disabling disease.

Central conducting lymphatic anomaly (CCLA)

This term describes a "channel-type" lymphatic anomaly of unknown etiology that includes a spectrum of rare lymphatic anomalies.

It is characterized by a dilation of the lymphatic vessels (also known as "cystic type lymphangectasia" or simply "lymphangiectasia"), caused by impaired motility of the lymphatic collectors or by obstructive mechanisms (functional or mechanical) of the more distal lymphatics, which involves impaired lymph flow resulting in lymphostasis.

Depending on the site, lymphostasis can be responsible for chylothorax, pleuro-pulmonary lymphangiectasia, in-

testinal lymphangiectasia with protein-dispersing enteropathy, chyluria, peripheral lymphedema, skin vesicles with superficial lymphorea.

For diagnostic purposes, dynamic MR lymphangiography with contrast medium is indicated and in expert hands, it allows to define the site of obstruction, the degree of collateralization and the extent of lymphatic reflux; this method is available only in very few centers in Italy.

Follow-up of CLM

Whenever there are signs and symptoms of bone involvement, whole body screening becomes necessary. In the absence of bone lesions, it is not necessary to do close checks. If we are faced with a GSD with progressive osteolysis, a radiological control is recommended every 2 months at least until the clinical picture is stabilized, obtained with therapy.

In GLAs and KLAs, the control can be annual, lacking progressivity and cortical involvement.

In all cases, early diagnosis of these diseases is crucial, as people experience significant morbidity due to frequent complications.

Cases of clinical onset at an early age, chylothorax, vertebral and rib bone localizations are indicative of a disease with poor prognosis.

INTERPRETATION OF THE DATA

To answer question 15, four articles were analyzed: an overview,[75] two narrative reviews,[74, 76] a protocol for a prospective multicenter trial.[77]

Taken together, the studies analyzed provide precise and homogeneous indications for the diagnosis of complex lymphatic malformation (CLM) and for the differential diagnosis of the various pathologies included in this group.

Since these are rare diseases and of unknown etiology, the first suspicion and the relative clinical-radiological orientation are almost always linked to a symptomatic triad: pain, spontaneous fractures, pleural effusion. This triad must guide the patient to promptly go to a reference center for vascular malformations.

Adequate studies describing CLM concern small series, however the clinical-instrumental information appears homogeneous and shared.

Recommendations

1. Faced with a clinical picture characterized by pain, spontaneous fractures and serous effusions, it is recommended that the patient be promptly sent to a reference center for vascular anomalies.

Recommendation of Good Clinical Practice, based on the experience of the panel

2. Whenever there are signs and symptoms of bone involvement, whole body screening becomes necessary.

Recommendation of good clinical practice, based on the experience of the panel

Differential diagnosis of CLMs

Question 16

What elements allow the differential diagnosis of the various types of Complex Lymphatic Malformations (GLA, KLA, GSD, CCLA)?

The differential diagnosis between GLA, GSD and KLA is based on instrumental investigations and biopsy.

Osteolysis is the most important element for the purposes of the differential diagnosis between the three forms, but the diagnosis of certainty requires a biopsy.

Cases of bone lysis confined only to the cancellous bone are classified as GLA; when cortical osteolysis is also present we speak of GSD, while we define KLA as the lesion that demonstrates the presence of spindle cells in the context of abnormal and dilated lymphatic vessels.

There is no familiarity for all three malformations.

Although it has to be considered a pathology of the lymphatic collectors ("channel-type" lymphatic malformation) and therefore embryologically different from other CLMs, the CCLA has clinical aspects sometimes superimposed on GLA and, especially in cases of thoracic localizations, the differential diagnosis can be difficult. In doubtful cases, dynamic MRI with contrast and intranodal lymphangiography are indicated.

INTERPRETATION OF THE DATA

To answer question number 16, an overview and a narrative revision were analyzed.

The studies analyzed provide uniform information that makes it possible to make the differential diagnosis between the various forms of CLM in the majority of cases. Considering the rarity of these malformations and the numerically modest case series, in diagnostic terms the risk of bias is to be considered high, even when the patient is correctly sent to a referral center.

Recommendations

1. Diagnosis of certainty of GLA, KLA and GSD always requires biopsy.

Recommendation of Good Clinical Practice, based on the experience of the panel.

2. In doubtful cases relating to the differential diagnosis between GLA and CCLA, the only diriment investigations are dynamic lympho-MRI with contrast and intranodal lymphangiography.
Recommendation of Good Clinical Practice, based on the experience of the panel

Treatment of MLC

Question 17
What are the possibilities for therapeutic treatment of CLM?

CLM therapy is always multidisciplinary and is based on the variable combination of drug therapies, surgery, radiotherapy, laser therapy and dietary measures.

Pharmacological therapies are based on the variable combination of off-label antiangiogenic drugs (vincristine, interferon-alpha-2, propranolol), cortisone, bisphosphonates (pamidronate, zoledronic acid), vitamin D, calcium, calcitonin,eotride and, more recently and with encouraging results, rapamycin (antilymphangiogenic mTOR inhibitor, also off-label drug). Dietary measures are often associated with drug therapy in the case of major effusions in the serous cavities, have very controversial value and consist of hypo-lipid diets and administration of medium-chain fatty acids.

Surgery is indicated in the treatment of chylous effusions, for the removal of pseudotumoral masses in KLA and, more rarely, it consists of personalized orthopedic procedures.

Surgical treatment of the chylothorax includes several possibilities: thoracic drainage placement, pleurocentesis, pleurodesis and pleurectomy, ligation or embolization of the thoracic duct, pleuro-peritoneal shunt with Denver valve.

Pleurodesis can also be performed with a sclerotherapic procedure (talc, doxycycline, tetracyclines).

When there are no surgical indications and there is evidence of disease progression despite drug therapies, there remains the possibility of radiotherapy, which in several cases has allowed pain control and arrested the spread of osteolysis; however, the risk of stunted bone growth and the onset of malignant tumor pathologies should be kept in mind.

None of the therapeutic procedures used areisive, as the goals are to stabilize the disease and prevent its progression, to reduce symptoms and to improve the quality of life. The management of these patients is strictly multidisciplinary and must take place at a qualified center.

The need for new therapies is absolutely evident.

About the recent use of rapamycin therapy, in a systematic retrospective study, the response to therapy was assessed in terms of radiological images, quality of life and clinical status.[78]

The study included 18 pediatric and young adult patients (13 with GLA and 5 with GSD).

In 15 cases (83%) there was an improvement in one or more of the 3 analyzed aspects (radiological improvement 28%, clinical improvement 83%, quality of life improvement 78%); in no case there was any worsening during therapy.

The article shows that oral rapamycin therapy is well tolerated and effective in improving symptoms and quality of life, although the evidence of radiological improvement is modest.

Adverse events were: bonerow inhibition, mucositis stomatitis, hypertriglyceridemia.

The suggested therapeutic dosage is 0.8 mg/m^2 twice daily, with adjustments aimed at maintaining blood levels of 10-15 ng/mL. Although the drug appears well tolerated, the long-term side effects are unknown, the optimal dose remains controversial and the duration of therapy is not yet clear.

Chronic inhibition of the mTOR pathway can cause glucose intolerance and insulin resistance, hypercholesterolemia and hypertriglyceridemia, and therefore the risk of cardiovascular events. Other potential problems, which need to be clarified, concern fertility, immunosuppression with the onset of malignant neoplasms, growth and somatic development.

INTERPRETATION OF THE DATA

To answer question 17, seven scientific papers were analyzed: a prospective single-arm multicenter trial,[53] two case series,[46, 75] a systematic review,[81] two narrative reviews,[78, 80] a case report.[79]

The studies analyzed show that the effectiveness of current therapies has not yet been validated by prospective clinical trials and is based on modest case series and narrative reviews.

All the therapies used are not curative, but palliative, with the aim of stopping or at least delaying the progression of the disease, reducing symptoms and improving the quality of life. The analyzed studies show how complex lymphatic malformations are burdened by progressivity and acute complications, and have a disabling character and sometimes even a poor prognosis. There are no effective therapies for these pathologies today.

In addition to the lack of adequate studies and uniform and shared protocols, it is necessary and imperative to promote research in the field of Complex Lymphatic Malformations.

Recommendations

The therapy of Complex Lymphatic Malformations is always of the multimodal type, and can be carried out and monitored only in specific multidisciplinary structures, and set on customized operational protocols, defined each time through joint discussion of individual cases.

Considering the difficulty of treatment and the modest results of the therapy, a close collaboration between the various structures, both national and foreign, is recommended.

Research recommendation

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Troncular lymphatic malformations: primary lymphedema

Definition and classification

Truncular lymphatic malformations of the limbs include primary lymphedema (LP) of the upper limbs (rarer) and of the lower limbs (in most cases), sometimes also localized (or exclusively localized) in the external genitalia, which develop in the final stages lymphangiogenesis, when the formation of lymphatic collectors and lymph nodes occurs.

These malformations be due to a condition of aplasia, hypoplasia or hyperplasia of the lymphatic vessels and lymph nodes, clinically manifesting as a state of obstruction or dilation, or with the absence or defect of the endoluminal valves, with a typical gravitational lymphatic reflux that represents the primary clinical manifestation.

These conditions of altered development or lymphatic dysplasia, if limited to the lymphatic collectors, can also be defined as lymphangiodysplasia (LAD I), to distinguish them from those limited to the lymph nodes, also referred to as lymphadenodysplasia (LAD II), as well as the mixed forms, described also as lymphangio-adeno-dysplasia (LAAD). The LAD II form is the most frequently encountered.

Depending on whether it manifests itself already at birth or later, before or after the age of 35, primary lymphedemas are classified into early connatals and late connatals; the precocious ones are distinguishable as sporadic or hereditary (with hereditary-familial transmission). Some gene mutations responsible for the forms of primary lymphedema reported in the Classification [1] approved by the "International Society for the Study of Vascular Anomalies - ISSVA" in its General Assembly (Amsterdam, 2018) have recently been identified (Table I).

In this way, primary lymphedema are more easily and properly differentiated from secondary or acquired lymphedemas, in turn divided into postsurgical, postactinic, postlymphangitic and parasitic.

Clinical pictures and staging

Primary lymphedema is associated with chronic distension of the limbs, secondary to the accumulation of lymph in the interstitial spaces, particularly in the subcutaneous tissues. It is related to a systemic or partial malformation of the lymphatic system.

The disease mainly affects women and usually affects one or both lower limbs (80%) and, less frequently, one

Table I.—*ISSVA classification for vascular anomalies.*

Simple lymphatic malformations	(Genetic anomalies)
Primary lymphedema	
Nonne-Milroy syndrome	*FLT4/VEGFR3*
Primary hereditary lymphedema	*VEGFC*
Lymphedema-distichiasis	*FOXC2*
Hypotrichosis-lymphedena-teleangiectasia	*SOX18*
Primary lymphedema with myelodysplasia	*GATA2*
Primary generalized lymphatic anomaly (Hennekam lymphangiectasia-lymphedema syndrome	*CCBE1*
Microcephaly with or without chorioretinopathy, lymphedema, or mental retardation syndrome	*KIF11*
Lymphedema-choanal atresia	*PTPN14*

upper limb, face or external genitalia. Onset is usually distal (at the toe level). Stemmer's sign (difficulty in grasping a skin fold on the dorsal part of the second toe) is strongly evocative of this pathology. The disease evolves with an increase in fibrosis and adipose tissues, while the liquid component (lymph)reases. Hyperkeratosis and papillomatosis be present. The main complication is erysipelas on the skin of the toes, or in other segments of the affected limb/limbs, or of the external genitalia.

The most modern staging responds to clinical and instrumental criteria (lymphoscintigraphy), to which immuno-histopathological criteria and the degrees of disability resulting from the worsening of the clinical picture must be added.

This staging refers to the official one of the Consensus Document of the International Society of Lymphology (ISL), more recently and partially modified, with the distinction in: Latent Lymphedema (Stage IA); Initial (Stage IB); Worsening (Stage IIA); Fibro-Lipo-Lymphedema (Stage IIB, with "column" limb); Elephantiasis (Stage IIIA); Extreme elephantiasis (Stage IIIB).

Stage I

IA - "Latent" lymphedema: absence of clinical signs of edema, but in the presence of an altered lymphatic transport capacity (demonstrable by lymphoscintigraphy) and with initial immuno-histochemical alterations of the lymph nodes, lymphatics and interstitial matrix.
IB - "Initial" lymphedema: totally or partially reversible with rest and sloping position, with progressive worsening of lymphatic transport capacity and immuno-histochemical alterations of the lymph nodes, lymphatic collectors and extracellular matrix.

Stage II

IIA - "Worsening" lymphedema: minimal lymphatic transport capacity (vanishing lymph transport capacity), recurrent attacks of acute lymphangitis, neo-lipogenesis, fibro-lipo-sclerotic skin changes and progressive functional disability.
IIB - Fibro-lipo-lymphedema ("column" limb): absence of lymphatic transport, with skin alterations on a lymphostatic basis and progressive disability.
Stage III
IIIA – Elephantiasis: absent lymphatic transport capacity, with indurative fibro-lipo-sclerotic pachydermitis, lymphostatic verrucosiform skin papillomatosis and severe disability.
IIIB - Extreme elephantiasis: totally disabling disability.

Epidemiology

Primary lymphedema can be congenital (less than 10% of cases), early onset (before age 35, 65-80% of cases) or late onset (after age 35, 10% of cases).

The prevalence of primary lymphedema is estimated in Europe at 1/10,000 inhabitants before the age of 20.[2]

Etiology

The etiology of primary lymphedema is unknown, but it is associated with dysplasia / aplasia / hypoplasia of the lymphatic tracts. In about 25% of cases, triggers can be identified: ankle sprain, pregnancy, overexertion, insect bite, etc. In less than 3% of cases, this pathology is familiar, such as Milroy's syndrome (congenital lymphedema with autosomal dominant transmission) or Meige's syndrome (early onset with autosomal recessive transmission). In these cases, mutations in the *VEGFR3* gene (Vascular endothelial growth factor receptor 3) have been identified in some families affected by Milroy's syndrome. In very rare cases, lymphedema is associated with other clinical abnormalities (distichiasis, ptosis) or be part of a complex syndrome: Turner syndrome, Klinefelter syndrome, Noonan syndrome (multiple congenital malformations similar to Klinefelter syndrome, but with a normal karyotype and with the same incidence in man - woman), Yellow-nails syndrome (lymphedema in a patient with yellow nails and bronchiectasis), intestinal lymphangiectasias, lymphangiomatosis. adenopathies, etc.

In primary lymphedema, at least one aberrance gene has been identified for all known forms (see ISSVA classification).

Diagnosis

Question 1
Are there clinical signs that distinguish primary lymphedema from other types of edema?

Primary lymphedema represent a chronic form of lymphedema, with variable onset in developmental age, generally little exposed to inflammatory events, which mainly affect the lower or upper limbs, mono- or bilaterally, sometimes with extension to the genitals.[1-5]

INTERPRETATION OF THE DATA

To answer question 1, a guideline,[1] 3 narrative reviews[2-4] and a series of cases[5] were identified.

The studies analyzed that report the clinical characteristics of primary lymphedema expose, as a whole, the semeiotics of primary lymphedema in an exhaustive and

didactic way. The quality of the evidence was assessed through non-analytical studies and was found to be fair.

Recommendation

For the clinical diagnosis of primary lymphedema, a thorough history of exclusion of further causes of lymphedema is indicated, in addition to the clinical finding of rhizomelic edema of a district (generally lower or upper limb), not painful to compression in the first stages, with the presence of fovea to digital compression.

Strong recommendation in favor, level of evidence 3-4

Question 2

What is the first-choice investigation for the diagnosis of primary lymphedema?

An accurate diagnosis of lymphedema is essential for appropriate therapy. In most patients, the diagnosis of lymphedema can be readily determined from medical history and physical examination. In other patients, confounding conditions such as morbid obesity, venous insufficiency, occult trauma and repeated infections can complicate the clinical picture. Furthermore, when considering the basis of unilateral limb lymphedema, especially in adults, occult visceral tumor obstructing or invading more proximal lymphatics should be considered. For these reasons, a thorough medical evaluation is essential before embarking on the treatment of lymphedema. Comorbid conditions such as congestive heart failure, hypertension, and cerebrovascular disease (including stroke) can also influence the treatment approach taken.[6-10]

The Echo-Color-Doppler is therefore important, as a first level examination, to verify the coexistence of a venous pathology, essential for the distinction of lymphedema in pure lymphedema and phlebo-lymphedema or lympho-phlebedema, depending on the predominance of one of the two components, lymphatic or venous, and being able to highlight the coexistence of an arterial component associated with the first two (artero-venous fistulas).[11]

INTERPRETATION OF THE DATA

To answer question 2, a systematic literature review,[6] three narrative reviews[7-9] and two observational studies[10, 11] were identified.

The studies analyzed show the agreement that color Doppler ultrasound is a highly sensitive and specific test, of first choice to confirm or exclude arterial and venous vascular pathologies concomitant with the clinical manifestations of primary lymphedema. It is a widespread, non-invasive, low-cost vascular examination, inserted as a first step in the diagnostic-therapeutic protocols of lymphedema. The analyzed studies are relevant for the target population.

Recommendation

The Echo-color-Doppler is not a specific exam for the study of primary lymphedema, but it is indicated as a first level exam for the differential diagnosis. It should be prescribed by a competent and experienced specialist in the diagnosis and treatment of lymphedema.

Strong recommendation in favor, level of evidence: 2 ++

Question 3

What are the most suitable investigations for the diagnostic confirmation of primary lymphedema?

The level I, II and III instrumental investigations can be summarized in Table III, which represents the most widely shared diagnostic algorithm in International Literature - EBM.

The diagnosis is based not only on the anamnesis and physical examination, but also on level I instrumental investigations, represented by Echo-Color-Doppler and Lymphoscintigraphy, which today are flanked by other investigations, including Lymphangio-Magnetic Resonance.

The diagnostic tool of isotopic lymphography (also called lymphoscintigraphy or lymphangioscintigraphy) has proved extremely useful in representing the specific lymphatic anomaly. Where nuclear medicine specialists are available, lymphangioscintigraphy (LAS) has largely replaced traditional oil contrast lymphography to visualize the lymphatic network. Although LAS has not been standardized (various radiotracers and doses of radioactivity, different injection volumes, intracutaneous *versus* subcutaneous injection site, epi or subfascial injection, one or more injections, different protocols of passive and active physical activity, variable imaging, static and / or dynamic techniques), the images, which can be easily repeated, offer a remarkable understanding of lymphatic (dis) function.[12, 13]

Lymphoscintigraphy currently represents the "gold standard" instrumental investigation and must be carried out for the comparative study of both superficial and deep lymphatic circulation, combining a quantitative evaluation by measuring the Lymphatic Transport Index (ITL) (normal from 1 to 9, pathological if >10).[14, 15]

LAS provides both images of lymphatics and lymph nodes, as well as semiquantitative data on radiotracer (lymph) transport and does not require skin injections of blue dye (as used for example in the visualization of the axillary or inguinal sentinel node, for example lymphad-

enoscintigraphy). The injection of dye is in fact occasionally complicated by an allergic skin reaction or severe anaphylaxis. Furthermore, the clinical interpretation of lymphatic function after the injection of vital dye alone ("the blue test") is often misleading.[16, 17]

INTERPRETATION OF THE DATA

To answer question 3, a systematic literature review[12] and five cohort studies[13-17] were identified.

In the studies analyzed, the experts agree on the execution of a lymphoscintigraphy as a suitable instrumental examination, for sensitivity and specificity, in the identification and characterization of lymphatic pathology in primitive lymphedema of the limbs and genitals. Lymphoscintigraphy is a minimally invasive test, but at risk of inducing allergic reactions and not recommended in children, in order to avoid the need for anesthesia or sedation of the child. The number of recent studies is limited, but the appropriateness of this survey is shared and consolidated as a pre-eminent specific survey for the diagnosis of primary lymphedema in the target population, with a prevalence of benefits over possible harm. The quality of the evidence was found to be acceptable, assessed through the checklist for systematic reviews and cohort studies. The analysis of the studies highlights a clear relevance for the target population, consistent conclusions and the absence of potential bias, so the recommendation that can be formulated is of a strong degree.

Recommendation

Lymphoscintigraphy is indicated as a specific first level examination for the study of primary lymphedema, which must be prescribed by the competent specialist doctor experienced in the diagnosis and treatment of lymphedema.
Strong recommendation in favor, level of evidence: 2 ++

Question 4

What other tests are used for the correct interpretation of primary lymphedema?

Lymphangium-MRI is today above all useful in the definition of kilo-lymphatic gravitational reflux on a malformative basis.[18]

Among the other level II instrumental investigations, Fluorescein Microlymphography and Direct Lymphography are of particular importance today.

The Indocyanine Green Fluorescein Microlymphography (Indocyanine Green-ICG Test) represents the overcoming of the traditional Lymphangioscopy or Blue Patent Violet Lymphochromic Test (BPV) and allows the mapping of the subcutaneous superficial lymphatic network.[19]

Direct or conventional lymphography, consisting in the visualization of the lymphatic tracts by direct injection of a liposoluble iodinated contrast medium (Lipiodol Ultrafluido) into the bipodal lymphatic collectors, prepared with microsurgical technique under the Operating Microscope, is advantageously combined with Computed Tomography (Lymphangio-CT)[20] for the diagnostic definition of primary lymphedema (or chylolymphedema), consequent to lymphatic (or chylous) gravitational reflux on a malformative basis.

Finally, for level III instrumental investigations, especially considering the possible venous and arterial malformation combinations with lymphatic ones, Phleboscintigraphy, Phlebography and Arteriography have an elective indication.

Genetic tests have proved increasingly widespread and feasible to define a limited number of peculiar hereditary syndromes with specific gene mutations[21-23] such as lymphedema-distichiasis (FOXC2), some forms of Milroy's disease (VEGFR-3) and telangiectatic hypotrichosylymphedema (SOX18).

The near future promises that such tests, combined with careful phenotypic descriptions, will become routine for classifying familial lymphangiodysplastic syndromes and other congenital/dysmorphogenic diseases characterized by lymphedema, lymphangiectasia and lymphangiomatosis. In addition, there are many other clinical syndromes with associated lymphedema: identifying genes also be found for these in the future.

The diagnosis can then also be completed by other imaging studies (Angio-CT or MRI) for a more accurate differential diagnosis with other causes of edema of the limbs (of cardiac or renal origin or hypoprotidemia), with lipedema (accumulation of adipose tissue starting from the hips up to the ankles in some obese subjects) and with local causes (venous edema) (Figure 1).

INTERPRETATION OF THE DATA

To answer question 4, three cohort studies[18-20] and three reviews[21-23] were identified.

Although there are not many studies to evaluate the scientific evidence of the role of second and third level methods, the analysis of the studies highlights a clear relevance for the target population, consistent conclusions, but the presence of potential bias.

Reccomendation

1. For the instrumental staging of primary lymphedema, imaging methods are also indicated (Lymphangium-MRI,

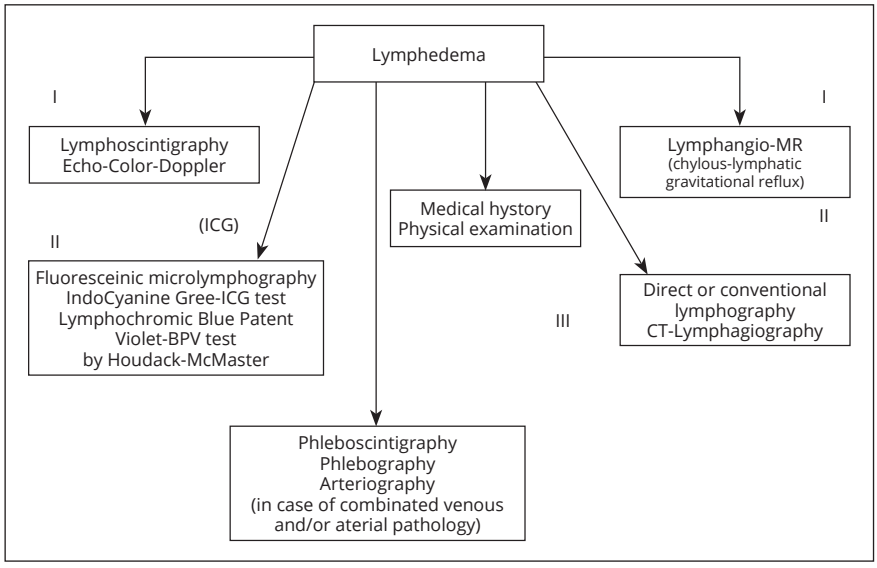

Figure 1.—Diagnostic algorithm (instrumental investigations of I, II and IIII level).

Indocyanine Green Fluorescein Microlymphography, Direct or conventional lymphography) which require a specialist request and whose specificity is linked to a correct investigation technique and experience of the operators.
Weak recommendation in favor, level of evidence 2-

2. The use of Genetic Tests is indicated in syndromic and familial forms and for research implementation.
Weak recommendation in favor, level of evidence 2+

Treatment

Question 5

What are the treatments to be included in conservative therapy for primary lymphedema?

The therapy of Primary Lymphedema of the limbs makes use of 2 types of treatment: non-surgical treatment and surgical treatment (Table II).

Non-surgical treatment is based on combined physiotherapy (CPT: combined physio-therapy) and pharmaco-phyto-therapy.

Multimodal combined physical therapy includes:

• "skin care" procedures (careful skin hygiene of the fingers of the extremities and of the external genitals);

• manual and mechanical lymphatic drainage (with devices with uniform intermittent andreasing disto-proximal pressure; with peristaltic-sequential pump; with intermittent negative pressure chambers and with non-invasive mechanical body massage);[24-26]

• multilayer functional bandages, isotonic muscle exercises and appropriate physical activity (bio-circuit remedial exercises);

• "life style" (healthy lifestyle habits and regulated diet).

The pharmaco-phyto-therapy involves the intake of Food Supplements, with natural extracts essentially based on Benzopyrones (Melilotus Officinalis - Coumarin), associated with Antibiotics/Antifungals (for the treatment and prevention of acute lymphangitis of bacterial origin and/or fungal).[27-33]

TABLE II.—*Therapy of the lymphedemas.*

Non-operative treatment
Multimodal combined physio-therapy (CPT: combined or complex physio-therapy)
Skin care
Manual and mechanical lympatic drainage
Multilayer functional bandages
Remedial isotonic exercises
Physical activity-Sports
Life style
Pharmaco-phyto-therapy
Antibiotics
Antimycotics
Dyethyicarbamazyne
Benzopyrons
Operative treatment
A) Functional surgical procedures
Derivative microsurgery (multiple lymphatic-venous anastomoses)
Reconstructive microsurgery (lymphatic-venous-lymphatic-plasty)
B) Reductive and exeretic procedures
Fibro-lipo-lymph-aspiration (venous and lymph vessel sparing procedure, Echo-Doppler and ICG-Test guided)
Debulking procedures

INTERPRETATION OF THE DATA

To answer question 5, two systematic reviews,[27, 30] six reviews[24, 26, 28, 31-33] and two cohort studies[25, 29] were identified.

Studies are relevant to the target population, consistent conclusions and no potential bias. The quality of the evidence, assessed through the checklist for systematic reviews and cohort studies, was found to be acceptable in both cases.

Recommendations

1. Multimodal combined physical therapy is indicated as a first choice therapy in the treatment of primary limb lymphedema, as it is free of side effects.
Recommendation of good clinical practice, based on the experience of the panel

2. Pneumatic compression is indicated in mild forms of lymphedema (stage I) and is effective only if inserted within the CDP (Combinedongestive Physiotherapy). It is of little efficacy when applied as an isolated therapy.
Weak recommendation in favor, level of evidence 2 ++

3. Pharmacological therapy represents an ancillary aid in the treatment of lymphedema, to be prescribed for limited periods, under medical observation.
Weak recommendation in favor, level of evidence: 1+

Question 6

What are the indications for surgical treatments for primary lymphedema?

The surgical treatment includes functional interventions and exeretic or reductive interventions.[33]

Functional interventions are based on the applications of microsurgery and are divided into 2 types:

• derivative microsurgery (multiple lymphatic-venous anastomosis);

• reconstructive microsurgery (lymphatic-veno-lymphatic-plastic), through the interposition between the lymphatics, upstream and downstream of the functional obstacle, of autologous valved venous grafts, taken from healthy sites, such as the volar surface of the forearm (segments of cephalic or basilica vein of variable length from 7 to 21 cm). This method is indicated, above all, in the treatment of primary lymphedema of the lower limbs associated with venous pathology, with superficial and deep venous hypertension. The autotransplantation or the transposition of 1 or more lymphatic collectors, as well as the lymph node autotransplantation, are methods of rarer application and still of value, above all, experimental.[34-37]

Exeretic or reductive interventions involve the application of plastic surgery methods, in order to reduce, as aesthetically as possible, the excess of fibro-adipose tissue, resulting from therease in lymphatic stasis induced by conservative surgery or functional surgery.

The most satisfactory results can be obtained with the application of a method similar to Liposuction, by tumescence, guided with the Echo-Color-Doppler mapping of the main superficial venous trunks and with the mapping of the superficial lymphatic network, obtained with fluorescein microlymphography with indocyanine green, thus creating a "Vein and Lymph Vessel Sparing" procedure, capable of preventing injuries to the lymphatic collector routes, especially those occurring close to the venous trunks. This method is called Fibro-Lipo-Lymph-Aspiration (FLLA).[38-40]

Surgical treatment, however, is indicated only in cases of evident failure of non-surgical treatment. Commonly the accepted time interval for the "timing" of surgical therapy is 6-12 months after a correct, but ineffective, application of non-surgical conservative treatment, which can be assessed through the degree of edema reduction and the consequent improvement in quality of life.[41-43]

INTERPRETATION OF THE DATA

To answer question 6, four systematic reviews,[33-35, 38] two reviews [36, 37] and five cohort studies[39-43] were identified.
Studies show that surgical treatments for primary lymphedema have selective indications and that the experience of the specialist team plays an essential role in the therapeutic indications, but there is still no definitive evidence about the long-term efficacy of surgical therapies. The quality of the evidence, sought through the Checklists for systematic reviews and cohort studies, was found to be good.

Recommendations

1. Resective surgical procedures have not yet received confirmation of effective results over time and are not without complications, as they can be selectively indicated in specialized centers.
Weak recommendation in favor, level of evidence 2 ++

2. Liposuction procedures can give short, medium and long term positive results in primary lymphedema, especially in the early stages.
Weak recommendation in favor, level of evidence 2 ++

3. Procedures of microsurgical derivation require selective indications and can give positive results in the short, me-

dium and long term in primary lymphedema. They must be proposed selectively in specialized centers and in the context of integrated treatments.
Weak recommendation in favor, level of evidence 2+

Question 7
What are the most effective means for maintaining the results obtained from conservative and/or surgical therapies for primary lymphedema?

Elasto-compression therapy with elastic bandages or braces[44] is indicated above all in maintaining the results of therapies for primary lymphedema of the lower limbs, in order to improve symptoms related to peripheral lymphatic stasis.
The use of orthopedic braces is useful for improving the functionality and quality of life in the forms associated with skeletal anomalies.

Physiotherapeutic treatments[45] can be helpful in selected cases. Manual and mechanical lymphatic drainage are indicated in conditions of intolerance to elastic compression.[46, 47]

INTERPRETATION OF THE DATA

To answer question 7, a consensus,[44] a review[45] and two expert opinions[46, 47] were identified.

The studies analyzed show that the effectiveness of current therapies has not been validated by prospective clinical trials and is based on consensus, narrative reviews and case series. Containment therapies using elastic braces are not curative but recommendable, albeit palliative, with the aim of halting or at least delaying the progression of the disease, reducing symptoms and improving the quality of life. The studies are to be considered relevant to the target population, the conclusions are consistent but there is a potential risk of bias, especially in consideration of the limited series.

Recommendations
The use of elastic limb braces during daily activities is important for maintaining the results of lymphedema therapy in the long term.
Recommendation of good clinical practice, based on the experience of the panel

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